Mapping the relationship between white matter and executive function across the adult lifespan

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MAPPING THE RELATIONSHIP BETWEEN WHITE MATTER AND EXECUTIVE FUNCTION ACROSS THE ADULT LIFESPAN

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Abstract

Executive function and some forms of memory have been observed to decline with age. These cognitive declines are often subtle and do not necessarily impede the ability of an individual to lead a perfectly fulfilling and independent life. However, a better understanding of what may influence these small deficits could contribute towards our understanding of what happens when executive dysfunction occurs with greater severity across different patient cohorts. Considerable work has already been done exploring these dynamics regarding cortical and subcortical regions, but white matter correlates are not so well understood. The aim of this study was to examine the relationship between the microstructure of frontal white matter pathways and age-related decline in three key cognitive processes associated with executive function (attention, working memory and planning).

Methods

104 healthy participants (18 – 79 years) were recruited for this cross-sectional observational study. Neuroimaging and behavioural measures were collected. Data from a subset of 18 participants was used to establish reliability of manual and semi-automated tractography protocols for the cingulum, corpus callosum, frontal aslant tract (FAT), inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF) system and uncinate fasciculus in young and older adults. Data a separate group of 86 participants (18 – 77 years) were then analysed to test for age related changes to tract microstructure, task performance and mediation effects of tract microstructure on age-related decline of cognition.

Results

Overall volume and HMOA measures from manual and semi-automated dissection protocols demonstrated good reliability in both young and older adult age groups except for the third segment of the corpus callosum, the right FAT and right IFOF. Significant age-related declines were observed across all behavioural measures and all tracts except for the posterior segments of the corpus callosum, right cingulum, bilateral SLFI, and left SLF II. Significant task/tract correlations were identified across several different pathways and behavioural measures. Three tracts (left cingulum, left IFOF and left uncinate) demonstrated either a partial or full mediation effect on age-related declines in performance of episodic memory and planning.

Conclusion

First, results from this study have established that manual and semi-automated dissection protocols are reliable for both young and older adults in a wide range of white matter pathways. Second, this study has described for the first-time ageing trajectories of the frontal aslant tract and SLF system. Lastly, this study has supported the role of the cingulum and IFOF in attention and working memory processes and has highlighted a potentially more prominent role than originally supposed for the uncinate in executive function.

Table of Contents

Table of Figures

Table of Tables

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Statement of work and contributions

I designed the study with support from my supervisors. The work of this thesis could not have been completed without access to a bespoke version of the Cambridge Brain Sciences neuropsychological test battery kindly provided by Adam Hampshire and his colleagues. As part of the wider study I received advice from the author of Change Detection (feature binding) task Dr Mario Parra which was included as one of the tasks within the overall neuropsychological battery. A proportion of the data (scan data) was from a separate study managed by Dr Flavio Dell'Acqua (24 participants). I managed the recruitment of the remaining data set with support from two researchers Alice Russell and Cerisse Gunasinghe. I set up the neuropsychological assessment battery and directly interviewed a percentage of participants and was supported by Etta Howells, and Cerisse Gunasinghe. Rosie and Helen also assisted in several interviews. I conducted all the analysis presented in the thesis.

All dissection protocols described in this thesis are based upon those practiced by the expert operators within the Natbrainlab.

Many of the figures were created by the author using the following resources: Screen shots from the Cambridge Brain Sciences online task repository; Whole brain image templates were accessed from Surf Ice (https://www.nitrc.org/projects/surfice/); Tracts were delineated using the protocols described in chapter 6 via TrackVis and Mega Track software; Adobe Illustrator was used to compile component images into the relevant figures.

A larger number of scans and tasks were included in this data set than have been reported in this Thesis. The complete list of behavioural and neuroimaging measures can be found in section 12.6 for interest and reference. Data from the overall battery has supported a number of publications (Howells et al., 2018; Parlatini et al., 2017; M. Thiebaut de Schotten et al., 2015). The anonymized scan data and a proportion of the behavioural measures has also been loaded onto a NeurOimaging DatabasE (NODE) using HIVE DB technology (Muehlboeck, Westman, & Simmons, 2014) and is available to King's staff and students for further analysis. Anonymized Spherical Deconvolution scans collected as part of this study have contributed to the development (in progress at time of writing) of an online tool to provide a standardized Atlas of white matter

tracts of healthy adults for the wider research community. Subsets of this data have also supported another PhD, and six MSc projects. I supported four of these six students in their MSc projects directly.

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Abbreviations

Abbreviation	Meaning
ACC	Anterior Corpus Callosum or Anterior Cingulate Cortex
AD	Axial Diffusivity
ADC	Apparent Diffusion Coefficient
ANT	Attention network task
BA	Brodmann Areas
CAD	Coronary artery disease
CADSIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CPT	Continuous Performance Test (measuring attention)
CST	Cortico-spinal tract
DAT?	Dementia of the Alzheimer's Type?
DLPFC	Dorsolateral prefrontal cortex
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
FAT	Frontal Aslant Tract
FEF	Frontal Eye Field
FOD	Fibre Orientation Distribution
HARDI	High Angular Resolution Diffusion Imaging
HMOA	Hindrance Modulated Orientation Anisotropy
IFg	Inferior frontal gyrus
IFOF	Inferior Fronto-Occipital Fasciculus
ILF	Inferior Longitudinal Fasciculus
MCI	Mild Cognitive Impairment
MD	Mean Diffusivity
MFg	Middle frontal gyrus
MMSE	Mini mental state exam
MPRAGE	Magnetisation Prepared Rapid Acquisition Gradient Echo
MS	Multiple Sclerosis
MTL	Medial Temporal Lobe
ODF	Orientation Distribution Function
PCA	Principal component analysis
PCC	Posterior Corpus Callosum or Posterior Cingulate Cortex
PPA	Primary progressive aphasia
RD	Radial Diffusivity
RPM	Raven's Progressive Matrices
SD	Spherical Deconvolution
SFg	Superior frontal gyrus
SLF	Superior Longitudinal Fasciculus
SLF/ARC	Tract interpreted as either the SLFIII or anterior segment of the arcuate
VLPFC	Ventrolateral prefrontal cortex
WAIS-R	Wechsler Adult Intelligence Scale

Chapter 1 Introduction

Executive function and some forms of memory have been observed to decline with age (Craik & Salthouse, 2011; Sorel & Pennequin, 2008; West, 2004; West & Alain, 2000). In healthy ageing these cognitive declines are often subtle and do not necessarily impede the ability of an individual to lead a perfectly fulfilling and independent life. However, a better understanding of what may influence these small deficits could contribute towards our understanding of what happens when executive dysfunction occurs with greater severity across different patient cohorts.

To do this, one must first identify what has already been established, and where the gaps of knowledge are. A considerable amount of research has already been undertaken to either identify the neural correlates of executive function or to examine how these change with age. However, much of this work has focused on the cortical and sub cortical regions of the brain and less has been done to explore the relationship of the white matter pathways connecting these regions together. Approximately half of the brain consists of white matter. Damage to its microstructure due to pathology has previously been demonstrated to play a critical role in cognitive dysfunction and its gradual decline in some regions of the brain has been shown to play a mediatory role in the decline of some forms of executive function in healthy ageing. Therefore, focus on the role of white matter tracts either not previously described, or not previously matched to specific cognitive processes would provide new information and insight to this field.

Next, certain challenges need to be addressed. For example, it is important to acknowledge that the cognitive construct of executive function is a complicated one. Notwithstanding the many different definitions of executive function out there, it is an umbrella term that encompasses many subcomponent cognitive processes. The emphasis of which combination or which single cognitive process best typifies executive function also varies. This is reflected in a range of different theoretical models used to describe the term. In order to explore the neural correlates of executive function, one must first clearly define what aspect of executive function is being measured and how.

A further challenge is the complexity of biological changes with age in the body and brain across the adult lifespan. To endeavour to unpick some of these intricately enmeshed and interwoven

variables is challenging to say the least. An overview of these changes, and an explanation of where the methods used to assess the trajectories of white matter ageing sit within this context is essential. New information from this research may bring new insights but will also have boundaries of interpretation. This will be addressed in relation to the findings of this study in the discussion.

1.1 Measuring white matter pathways

With the advent of and Diffusion Tensor Imaging (DTI) (Basser, Mattiello, & LeBihan, 1994; Le Bihan & Breton, 1985), based on Diffusion Weighted Imaging (DWI), it has become possible to measure the net movement of water molecules through the process of diffusion in brain tissue. In the brain, different tissues are organised structurally in different ways. The grey matter of the cortical and subcortical regions largely contains neuron cell bodies where water molecules (which left to their own devices, would move in a random motion) have greater freedom within which to travel. In white matter, which consists largely of neuron axons, (commonly long narrow structures wrapped in myelin), water molecules are forced to travel within the confines of a more compact and restricted microstructure. Using these principles, white matter microstructure can be indirectly measured by indices such as Fractional Anisotropy (FA) and Mean Diffusivity (MD). Fractional Anisotropy represents the degree to which water molecules travel in one direction relative to many directions – I.e. the 'directionality' of the tissue. This can be interpreted as an indirect measure of tissue organisation. Low FA (0) represents water molecules travelling randomly with no direction, whereas high FA (1) represents water molecules restricted to travelling along one axis only, thus indicating very compact, organised tissue.

The technique of deterministic tractography, where specific bundles of axons characterised as 'white matter pathways or tracts' are delineated using anatomically defined regions of interest provides a unique insight into the 3D structural lay out of the brain. However, the manual delineation of these regions of interest can be time consuming and requires expert anatomical knowledge. Atlases have been produced to give guidance on the manual positioning of these regions of interest at the correct anatomical landmarks (Catani & Thiebaut de Schotten, 2008, 2012; Oishi, Faria, Van Zijl, & Mori, 2010; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori,

2004). There are also some semi-automated methods being developed to help reduce the time taken to conduct tractography across large data sets.

There are still some limitations to DTI though. Where white matter pathways travel closely together or cross paths, the technique on occasion fails to accurately differentiate between the two proximal tracts. This can lead to a misrepresentation of the tissue architecture.

One approach to address this limitation has been the use of High Angular Resolution Diffusion Imaging (HARDI) imaging in combination with Spherical Deconvolution algorithms (Dell'Acqua et al., 2010; Tournier, Calamante, Gadian, & Connelly, 2004). HARDI works by gathering data on an increased number of directions in which water molecules can diffuse within a given space (voxel). This combination of methods provides greater granularity when describing tracts that are proximal to or crossing one another (Dell'Acqua, Simmons, Williams, & Catani, 2013). This has enabled in vivo visualisation and quantification of pathways associated with the frontal lobe in humans like the frontal aslant tract and superior longitudinal fasciculus system (Catani et al., 2012, 2013; Thiebaut de Schotten, Dell'Acqua, et al., 2011) that previously, due to their location were not accessible to accurate and effective recreation from diffusion data. Furthermore, the development of a semi-automated method to delineate tracts across large data sets enables work to be done at a potentially more efficient pace (Dell'Acqua et al., 2015). These new methods promise significant advantages in this field. However, the level of detail in the literature describing the delineation of these pathways is sometimes limited and can vary considerably from research group to group. Focus on testing the reliability of these protocols tends also to be on a single age group (e.g. young healthy adults). Whilst the measurement of a protocol in one population sample is a useful exercise, it does perhaps suggest limitations for its application to a wider range of investigations. Therefore, part of this thesis addresses this by using a subset of the neuroimaging data to systematically test reliability of manual and semi-automated dissection protocols in both young and older adults (see Chapter 4 and Appendix F).

1.2 Defining executive function

As mentioned earlier, executive function is a term used to describe a complex set of sometimes separate, sometimes interrelated cognitive processes that support goal directed behaviour. A consistent definition of executive function is difficult to pin down in the literature. According to (Stuss & Knight, 2013) it 'is a generic term that refers to a variety of different capacities that enables purposeful, goal-directed behavior, including behavioural regulation, working memory, planning and organizational skills, and self- monitoring' (Stuss & Benson, 1986). An alternative perspective comes from Lezak who suggests that executive function supports 'appropriate, socially responsible and effectively self-serving adult conduct' (Lezak, Howieson, Loring, & Fischer, 2004). Lezak goes on to outline four stages of executive function, volition (or goal formation), planning, purposive action and effective performance.

A list of the cognitive processes that fall under the umbrella term of executive function varies in the literature. Similar to Stuss and Benson's definition, components most commonly described are attention, working memory, cognitive control, cognitive flexibility, decision making, planning and problem solving (a brief definition of these terms can be found in panel 1). It is important to be mindful that some of these cognitive processes are umbrella terms themselves or may overlap with or be dependent upon one another. For example, both working memory and attention have several different forms, and both are required in order to be successful in decision making, planning and problem solving. In the literature, tests measuring just one of these processes are sometimes interpreted loosely to represent executive function in its entirety.

Two theoretical models of executive function have been referenced to direct the development of specific research questions for this study (see panels 2 and 3). The model proposed by (Baddeley & Hitch, 1974) presents an interplay between two distinct modalities of working memory (visuospatial and verbal) and an control system they termed the 'central executive'. In this model (described in more detail in panel 2) the central executive represents processes such as attention, cognitive control and flexibility, all of which are required to be able to generate plans, make decisions and solve problems, but it cannot operate without support from working memory. In the Supervisory Attentional System describe by (Shallice, 1982), the ability to perceive incoming information and demands, translate these into specific goals and prioritise them according to

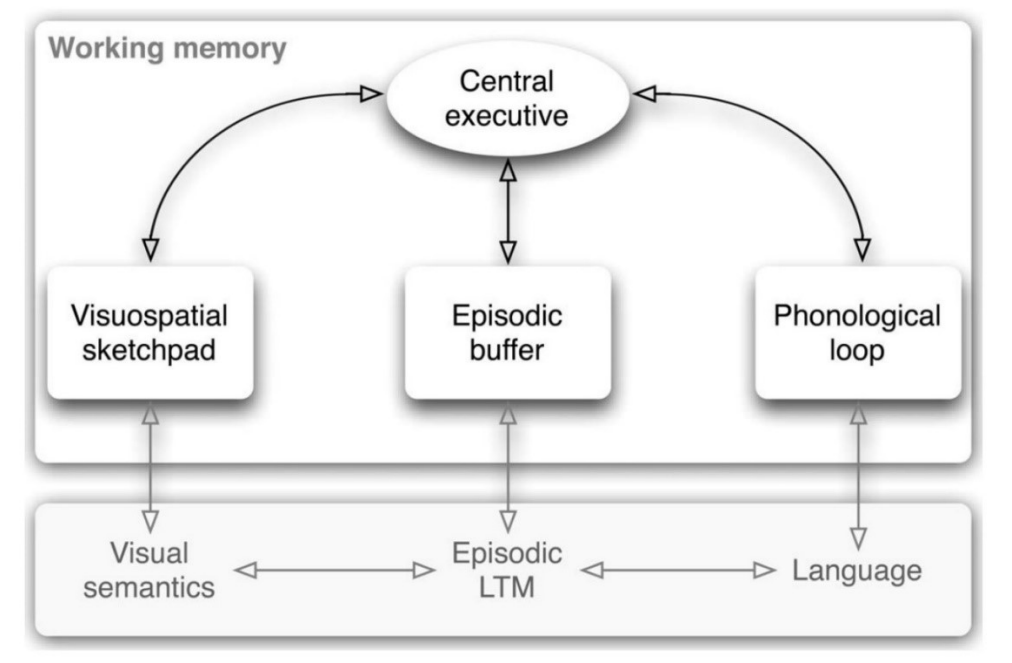
current context emphasises the cognitive process of attention. However, in order to prioritise one goal above another efficiently, the cognitive process of control also plays a significant role (see panel 1). While both models are very different, they agree on the idea that executive function consists of several interrelated components and that some of these components, such as attention and working memory, are pre-requisites for the successful completion of more complex operations.

Panel 1: Overview of cognitive processes associated with excutive function

Cognitive process	Description
Attention	Attention describes the ability to sustain focus on a given external or internal stimulus. (Mirsky, Anthony, Duncan, & Ahearn, 1991) describe several different forms of attention: 'focusing, sustaining concentration of vigilance, switching attention, distractibility, modulating the intensity of attention and attention to memorial processes such as rehearsal, retrieval and coding'
Working memory	Working memory is the ability to retain or even manipulate several small pieces of information in the mind for a short period of time. (Smith & Jonides, 1997) describe working memory as 'critical because it presumably serves as a mental blackboard for computations used in higher-level processes such as reasoning, problem solving, and language understanding'.
Cognitive flexibility	The ability to change your mind or behaviour in response to new information or changed circumstances.
Cognitive control	The ability to override prepotent behaviour or the desire to change course if that prepotent behaviour or change will take one away from one's current goal.
Planning and problem solving	The ability to plan is essential for goal directed behaviour. It involves the identification and sequencing of various steps or activities in the correct order to enable transition from a current situation to a goal situation. (Hayes-Roth & Hayes-Roth, 1979) describe it as 'the predetermination of a course of action aimed at achieving some goal.'
Decision making	The ability to weigh up the potential costs of doing something versus the potential rewards.

Panel 2: Overview of the psychological model of Executive Function proposed by Baddeley and Hitch

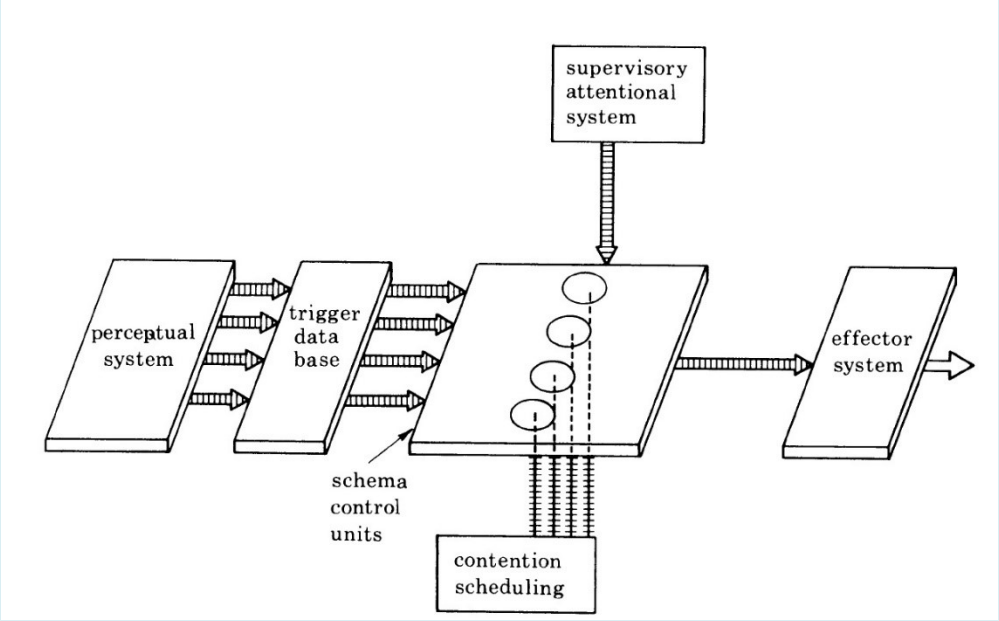
The Central Executive



The central executive (CE) hypothesis was originally introduced as part of multi component model to explain working memory (Baddeley & Hitch, 1974). Baddeley developed this further by proposing that four subcomponents were managed by the CE. These were focus of attention, dividing attention, switching attention and connecting between working memory and long term memory (Alan Baddeley, 1996). The model itself was later expanded to include an interface between an attentional control system (the central executive) two working memory components (the phonological loop and visuo-spatial sketch-pad) an episodic buffer and three other cognitive processes associated with long term storage of information (Repovs & Baddeley, 2006). Baddeley suggests that this multicomponent model is largely compatible with the Supervisors Attentional System (SAS) of Shallice and Norman (Shallice, 1982) (see panel 3).

Panel 3: Overview of the psychological model of executive function proposed by Norman and Shallice

The Supervisory Attentional System



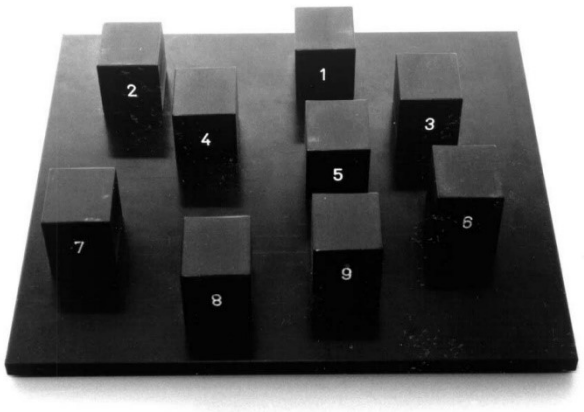
Proposed by Norman and Shallice in 1982 the Supervisory Attentional System (SAS) describes what they term 'an information processing model' of executive function. They describe basic learnt behaviours or thought patterns called 'schemas'. An example of a schema is an '*overlearned action or skill such as drinking from a container, doing long division, making breakfast, or finding ones way home from work'* (Shallice, 1982). In my personal experience, I would have to confess that long division is not a well-developed schema of mine, but making coffee certainly is. These schemas can be triggered by a perceptual cue (external or internal) or from the outcome of another schema. Shema's can be independently activated and thus a bottle neck of schemas' can result due to limitations on cognitive processes. It is here that the contention scheduling and SAS processes come into play. The contention scheduling process is a basic conflict resolution tool that uses crude criteria such as order of arrival or level of importance to prioritise schemas. It is a 'quick and dirty' approach to organising the load. As a secondary process, the SAS comes in to play particularly when prioritisation and organisation of schemas is required in relation to a novel situation, or a more complex sequencing of steps needed in order to solve a problem within the current context. It ensures that some schemas are postponed until a better time for them to operate appears, and identifies errors and corrections required to ensure the relevant goal is achieved. When deficits exist in this SAS, Norman and Shallice argues that executive disorders such as disinhibition are possible.

One of the most complex operations of executive function is that of planning and problem solving. The ability to plan is essential for goal directed behaviour. It involves the identification and sequencing of various steps or activities in the correct order to enable transition from a current situation to a goal situation. To do this, internal representations of current and goal situations need to be maintained in the mind's eye. Working memory is crucial for this. A comparison between the current and goal situation needs to be made and a list of possible sub goals or steps to 'fill the gaps' need to be generated, sequenced and evaluated. This process of evaluation will inevitably result in the rejection of some ideas, and the acceptance of others. Thus, decision making is required, as is cognitive flexibility (one must let go of one idea if it is proving unsuccessful in order to consider a new one that may produce the required result). To be able to sustain focus throughout this process, attention is essential.

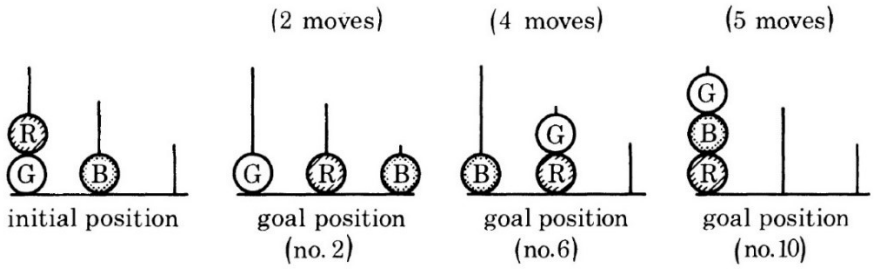
Over the years, three tasks have been introduced and become established measures of forms of attention, working memory and planning and problem solving. The Corsi Block Tapping task measures spatial working memory. The Stroop task measures a form of selective attention. The Tower of London task quantifies a form of visuospatial planning ability. Computerised versions of these task have been designed and provide an ease and efficiency to implementing these measures across study cohorts.

Blue
Green
Yellow
Green
Red
Blue
Purple
Green
Red
Blue
Yellow
Green
Purple
Blue
Red
Green

- example of the Stroop task



- example of Corsi block tapping task (Kessels, 2001)



- example of Tower of London task (Shallice,1982)

Figure 1 Examples of the a) Stroop, b) Corsi Block Tapping and c) Tower of London tasks.

A computerised battery of tasks measuring executive function developed by the Cambridge Brain Sciences Unit were used by (Hampshire, Highfield, Parkin, & Owen, 2012) to identify whether or not they were associated with single or multiple networks of brain regions. A small group of 16 healthy young adults performed 12 different tasks representing different cognitive processes associated with executive function during an fMRI scan. Using regions of interest associated with multiple demands identified by (Duncan & Owen, 2000) in previous studies, Principal Component Analysis was run to identify patterns of brain activation across the various tasks. They identified two different brain networks, a 'short term memory' network where tasks classically associated with working memory had more affinity for, and a 'reasoning' network where tasks classically associated with more complex cognitive processes such as reasoning, planning and problem solving were aligned to. Three of the tasks included in this study (spatial span, self-ordered search and paired associated) mapped most closely to the short-term memory network and the

other three mapped more closely to the reasoning component). These same 12 tasks were also made available to the general public in order to gather a large 'normative' data set across a broad range of ages. Using a vast sample of 44,600 internet users (aged between 12 and 70 years of age) a separate PCA analysis with orthogonal rotation identified not two but three latent factors or components. When observing the characteristics of the particular tasks that loaded more heavily on each component, these components were subsequently described as 1) Short term memory (i.e. working memory), 2) Reasoning and 3) Verbal. The computerized task based on the Corsi Block Tapping paradigm loaded onto the short-term memory component. The colour-word remapping task based on the Stroop task mapped most heavily onto the verbal component and the spatial planning task, based on the Tower of London paradigm mapped most closely to the reasoning component from this analysis (see table 7 in section 3.3.4).

What does the work conducted by (Hampshire et al., 2012) tell us about the neural correlates of executive function? It suggests that different cognitive processes involved in executive function can be grouped together and that these groups may be associated with separate brain regions or networks. However, there are some limitations. The networks were based on a selection of brain regions restricted by (Duncan & Owen, 2000) to the frontal and parietal lobes. Whilst the definition of these regions was based on sound empirical evidence, there is much in the literature to now question whether other regions may also be involved. In addition, the neuroimaging methods used by (Hampshire et al., 2012) were based on cortical and subcortical activation patterns from functional MRI in a relatively small data set of young healthy adults. The work did not include investigation into white matter pathways connecting these regions together, nor did it include older adults in its cohort. An opportunity then arises for this work to be expanded upon to examine white matter pathways of interest in a larger cohort including healthy adults across the adult lifespan.

1.3 Neurobiological aging

Our current understanding of neurobiological ageing describes the following patterns of change. By 18 years of age, our brain has already reached its maximum volume and has commenced a gradual decline which will continue into old age. There are some mixed reports in the literature as to exactly when peak brain volume occurs – ranging from mid childhood – (5 - 8 years of age) (Jernigan, Press, & Hesselink, 1990; Lebel et al., 2012) through to mid adolescence (12 – 15

years of age) (Courchesne et al., 2000), although most agree that once this decline does occur, it is linear in nature up until the 70's and 80's. By this point, the brain it has lost around a quarter of its original peak volume.

As the different tissues within the brain are separated out, different aging trajectories are uncovered. Cortical grey matter reaches peak thickness earlier than whole brain volume, at between 4 – 7 years of age, after which it declines in a curvilinear fashion (Lebel et al., 2012; Pfefferbaum et al., 1994). For example (Pfefferbaum et al., 1994) recruited 161 healthy subjects (male and female) between 3 months to 70 years of age. The group found that cortical volume peaked at 4 years of age, then decreased in a curvilinear fashion of on average 0.7ml a year. Alternative results have been presented by other groups. Two studies observing subjects ranging from 19 months to 80 years and 17 to 79 years of age respectively reported a linear pattern of grey matter volume decline with age (Courchesne et al., 2000; Good et al., 2001).

Within this overall decline, it appears that some grey matter regions are impacted more than others. The frontal cortices seem to be affected most, followed by smaller changes in the association regions of the temporal and parietal lobes (Fjell et al., 2009; Raz et al., 2005; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Sub cortical gray matter regions such as the basal ganglia and thalamus also seems to follow slightly accelerated aging compared to other regions (Li et al., 2014; Ziegler et al., 2012).

White matter volume takes the longest to develop, with some tracts reaching their greatest volume as late as in their 30's – 40's (Bartzokis et al., 2001; Courchesne et al., 2000; Lebel et al., 2012). As with grey matter there are regional variations in the developmental and aging trajectories. Frontal and superior parietal white matter seems to have the strongest age related decreases in volume (Brickman et al., 2006; Jernigan et al., 2001; Raz & Rodrigue, 2006; Resnick et al., 2003).

Last but not least, the 4 fluid filled ventricles of the brain gradually increase as the solid tissue of the brain atrophies. In their review (Raz & Rodrigue, 2006) reported lower average rates from 4 separate studies as 0.43% increase in volume per year. In comparison, for adults over the age of 70 a range of 2.90 – 5.96% increase in volume per year was reported from 5 different papers.

In terms of white matter microstructure, the length of time for tracts to fully mature is much longer than that of cortical gray matter. Depending on the region or specific tract, FA reaches peak value between 20 – 42 years of age, and MD reaches its lowest value between 18 – 41 years of age (Lebel et al., 2012).

In early studies, broad regional differences in aging trajectories were revealed and tended to focus largely on changes at a lobar level. One particular aging pattern described has been a differing degree of white matter microstructure decline from anterior (frontal and parietal) to then posterior (occipital) parts of the brain with age (Pfefferbaum et al., 2000). This resulted in the theory that regions that take the longest to mature, are the most vulnerable to aging degeneration. Studies investigating the corpus callosum have supported this theory (Abe et al., 2002; Pfefferbaum et al., 2000). An increase in white matter hyperintensities (WMH) have also been observed in healthy (non-symptomatic) older individuals, particularly in the frontal lobes (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Fazekas et al., 2005).

In support of this 'last in first out' hypothesis, a study examining 14 young adults (aged between 18 – 20 years) and 14 older adults (aged between 63 – 72 years) found larger age related changes to white matter microstructure in frontal compared to posterior regions (Bennett et al., 2010)

More recent studies have started to map the trajectories of individual white matter pathways. In a large study measuring volume, FA and MD for 9 different tracts (including segments of the corpus callosum) in 403 healthy individuals aged between 5 to 83 years of age, (Lebel et al., 2012) found significant age related changes for all pathways. However, rates of change varied. The fornix, genu and splenium of the corpus callosum were the earliest to reach peak FA. The fornix was also the first to reach lowest MD. The cingulum on the other hand took longest to mature.
In a study focusing on the 'oldest old' 94 subjects aged between 90 - 103 years of age (Bennett et al., 2017) were observed to exhibit significant age related changes in FA in the cingulum, corpus callosum, fornix and external capsule.

1.4 Theories of (neuro)cognitive ageing

There are several different theories of neurocognitive ageing currently discussed in the literature. Several are based on findings from functional neuroimaging studies and explore changes in regional activation during task completion (Overviews of each model are provided in Appendix B). Another model explores how a decline in one unified factor (processing speed) can impact all other cognitive processes or examine the relationship between structural changes in the brain and their cognitive correlates (See Appendix B). Two other models are based largely on structural neuroimaging studies and are most relevant to the scope of this study. These are the models most relevant to investigation of white matter changes with age and are described in more detail below.

In the frontal ageing hypothesis it was suggested that functions such as interference and cognitive flexibility rise and wane with development and then older age and that these functions are closely associated with the frontal lobe, which '*is also the last region of the brain to develop and appears to be the first to undergo involution later in life' (Dempster, 1992).* This theory was expanded and consolidated several years later to include retrospective and prospective memory functions (West, 1996).

Suggesting an alternative view (Greenwood, 2000) argued that changes to the frontal lobe with age are not as different to other regions of the brain and that decline in cognitive functions with age is more likely to be down to changes in a network of multiple brain regions than isolated to only the frontal lobe. In defence (West, 2000) explained that the frontal aging hypothesis does not negate aging of other brain regions, merely highlights that the frontal lobes are perhaps the earliest regions to begin degeneration and the hardest hit.

Subsequent research has begun to suggest that the frontal lobe hypothesis may operate in partnership with other phenomena. Researchers (Bugg, Zook, DeLosh, Davalos, & Davis, 2006) recruited 166 healthy subjects (aged between 20 – 89 years, mean 23.8 ± 2.1) who completed tasks to measure fluid intelligence, processing speed and what they termed 'frontal function' using tasks such as the Wisconsin card sorting and Tower of London tests. They found a significant decline in fluid intelligence with age. Using hierarchical regression, they demonstrated

that a significant proportion of the change in fluid intelligence was influence by processing speed, but that once processing speed was controlled for there were other factors that still influenced a decline in fluid intelligence. Suggesting that frontal function may still play a role.

A growing number of multimodal studies integrating fMRI and structural data are starting to appear in the literature. With them comes the theme of neurocognitive aging as a form of 'disconnection' (Antonenko & Floel, 2014; Madden et al., 2017a). For example, (Fjell, Sneve, Grydeland, Storsve, & Walhovd, 2017) recruited 119 young (aged between 19 – 53 years) and older adults (aged between 63 – 86 years) in a longitudinal study to test whether or not disconnections are directly the cause of a decline in cognition. They found that over 3.3 years, 82.5% of decline in executive function with age was explained by reduced *structural* rather than functional connectivity.

The idea that the frontal lobes and possibly other association cortices are more sensitive to age associated degradation of white matter tissue provides a useful anchor point from which to ask specific research questions. White matter pathways originating or terminating the frontal lobes are therefore of primary interest. Investigating the relationship between how changes to these frontal pathways influence the decline in certain executive processes with age and whether or not different sets of pathways (or networks) are found to influence different groups of cognitive processes would add to our current understanding in the field.

1.5 Mediation analysis

Previously mediation analysis has been used to probe the interplay between changes in age, executive function and brain structure. Mediation analysis is useful because it allows us to test whether the relationship between an independent or predictor variable (e.g. age) and a dependent or outcome variable (e.g. executive function) is significantly influenced by changes to a third variable (e.g. white matter microstructure) (see Fig.2). According to (Baron & Kenny, 1986) for one variable to be said to provide a significant mediatory or causal influence on the relationship between two other variables, certain pre-requisites are necessary; First, there should be a significant correlation between predictor (age) and outcome (executive function) variables (the 'direct' path c, Fig. 2). Second, there should be a significant correlation between the predictor (age) and the proposed mediator (e.g. white matter microstructure) variable (path a, Fig.2). Third,

the mediator variable should significantly predict the outcome variable (path b, Fig 2). Fourth, in a regression model that includes predictor, outcome *and* mediator (the 'indirect' path c', Fig 2), the predictor should influence the outcome variable *less strongly* than in path c. For example, (Madden et al., 2009) used this approach and found that changes in FA of frontal (genu) and parietal (splenium) sections of the corpus callosum played a significant mediatory role on the relationship between age and a decline in performance of a task switching paradigm (measuring a form of attention).

An alternative or supplementary measure of mediation is to report an *indirect effect* and its significance. The PROCESS plug in tool (Hayes, 2017) allows SPSS to calculate the indirect effect of a mediator variable using bootstrap methods which provide a robust approach for reasonably small samples sizes. The advantage of using the indirect effect as a metric is that it provides visibility of the *degree* of mediation observed in the data rather than just to affirm that mediation has occurred.

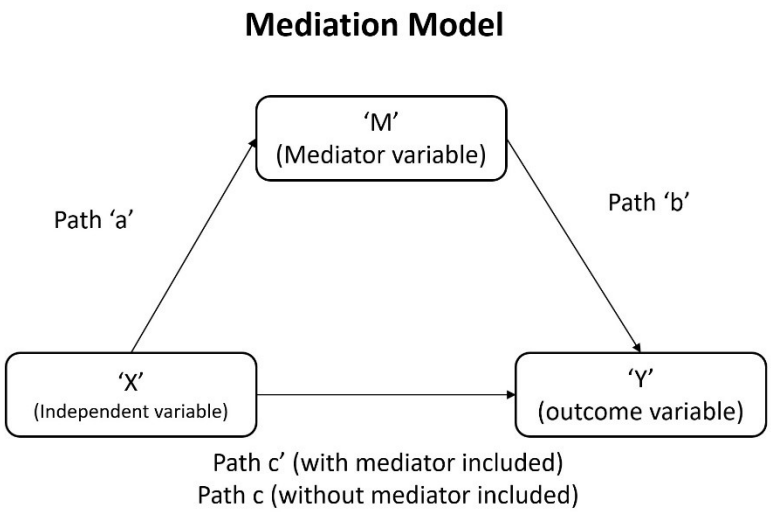


Figure 2 The mediation model

For this study, the Baron and Kenny causal steps method of reporting results were supplemented with the bootstrap BCa confidence interval method.

To summarise, executive function is known to decline with age. Three key cognitive processes well established in the literature as required for or characteristic of executive function are attention, working memory and planning. Alongside this, age related decline in the white matter microstructure of the frontal lobes has been associated with a decline in these very same cognitive processes. But evidence that specific pathways forming discrete networks may support certain cognitive processes is not yet comprehensive. A literature review was conducted to identify tracts of interest that could reflect distinct networks supporting each cognitive process (attention, working memory and planning). A reasonably large number of tracts were identified. Instead of running multiple mediation analysis for each pathway per cognitive task, we used preliminary tests in line with the logic of (Baron & Kenny, 1986) to produce a shortlist of 'candidate' tracts with which to run the mediation analysis.

A description of the literature review conducted, and the three main research questions identified is provided in the following sections. In addition, in recognition of the complexities involved in brain structure, executive function and neurobiological ageing, exploratory analysis was run on a slightly broader range of frontal lobe tracts and three additional measures of executive function to provide an overview of the data set within which these nested research questions were positioned. To support this analysis a discrete piece of work testing the reliability of both manual and semi-automated dissection protocols on tracts selected for this study was also conducted.

1.6 Literature search

Structured literature searches were conducted to provide an up-to date information regarding either a) reliability of tractography protocols or b) changes with age to executive function and / or white matter pathways of the frontal lobe with age:

i. Details of a hand search regarding reliability of tractography protocols are provided in Appendix A.
ii. The main search concerning executive function, white matter pathways of the frontal lobe and ageing was conducted initially in 2013 then updated in 2018. Details of the search terms used are provided in Appendix A. A final updated and expanded search was then in 2019. Details of the final expanded search conducted Apr 2019 are as follows:

The search was conducted using PubMed, Scopus and OVID. Keywords used were “executive function, cognitive control, attention, response inhibition, cognitive flexibility, working memory, planning, problem solving, decision making, Tower of London, Corsi Block Tapping, Stroop, white matter, DTI, Diffusion Tensor Imaging, Diffusion Weighted Imaging, DWI, Fascicles, Connections, Pathways, Spherical Deconvolution, SD, TBSS, Brain.

Inclusion Criteria: Search dates were restricted to 1st January 2013 – 31st March 2019.Publications in English, inclusion of adults (over 18 years of age),

Exclusion Criteria: Review articles, case reports, studies focused primarily on children; studies with a focus on genetic or cellular mechanisms, animal or pre-clinical studies.

Study screening process: A total of 1822 records were identified in this search, of which 280 were duplicates. From the remaining 1542 records, 1087 were removed after a brief title check. 453 abstracts were then checked, of which 71 were selected to be read in full. Of the remaining records, 27 were deemed of relevance and included in the current study.

A flow chart of the literature screening process can be found in Appendix A.

1.7 Research questions

1.7.1 Ageing, white matter and selective attention

1.7.1.1 Selective attention

Attention is a cognitive process that is most commonly identified with the ability to sustain focus on a given external or internal stimulus. However, attention can be applied or directed in different ways. For example, (Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991) list several different forms of attention as: 'focusing, sustaining concentration of vigilance, switching attention, distractibility, modulating the intensity of attention and attention to memorial processes such as rehearsal, retrieval and coding'. Another form called selective attention combines the ability to sustain concentration with selecting the most appropriate stimuli to respond to over other stimuli presented at the same time. This first research question focuses on selective attention.

1.7.1.2 Measurement of selective attention

In 1935 Stroop proposed a way to measure selective attention that has since become a task used widely used in experimental research studies (Stroop, 1935). During the Stroop task, the subject is asked to follow a simple rule which is to read out loud the colour of the ink of the word in front of them. The ease and thus rate at which a subject can follow this rule however, changes when the actual word itself spells out a colour that is incongruent to the colour of the ink it is printed in. For example, a word may be spelt BLUE but coloured RED, like this: **BLUE**. One popular theory of why this happens is that the subject experiences interference (and thus a slowing of response time) when the colour conflicts with the more automated process of reading the word. It is the ability of the subject to select the most appropriate stimuli and then inhibit or override an incorrect response that places the Stroop task among one of the more commonly used measurements to represent executive function. Computerized versions of this task, such as the one designed by (Hampshire, 2015) are now also available to use. For more details of this task see section 3.3.4.

1.7.1.3 Neural correlates of selective attention

Performance on Stroop type tasks is impaired in patients with frontal lobe damage (Stuss & Benson, 1984). Early PET studies using the Stroop task identified activations in the anterior cingulate gyrus, frontal polar cortex and some sub cortical (thalamus) or posterior regions (inferior

parietal cortex and lateral extra striate cortex) (Bench et al., 1993; Carter, Mintun, & Cohen, 1995). From other functional neuroimaging studies, a focus in the literature concerning the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex has become apparent. In their review, (Bush, Luu, & Posner, 2000) described a meta-analysis of 64 neuroimaging studies that identified activations of the dorsal section of the anterior cingulate cortex in Stroop and strop like tasks as well as other tasks requiring divided attention, verbal and motor response selection and working memory. From subsequent literature evidence of involvement of the DLPFC and anterior cingulate in selective attention continues to be reported (Floden, Vallesi, & Stuss, 2011; Krueger et al., 2011; Mathis, Schunck, Erb, Namer, & Luthringer, 2009; Puente, Faraco, Terry, Brown, & Miller, 2014; Rizk et al., 2017; Song & Hakoda, 2015; Tsuchida & Fellows, 2013) . A smaller number of studies have also implicated other regions such as the brain stem and parietal, occipital and temporal lobes with this form of attention (Kikuchi et al., 2012; Puente et al., 2014).

Diffusion imaging studies have begun to extend our knowledge from fMRI findings by examining broad regions of white matter tissue associated with these cortical regions of interest. For example, one study looking at diminished Stroop performance in older adults with major depression observed correlations between task scores and FA in white matter proximal to the anterior and posterior cingulate as well as prefrontal, insular and para-hippocampal regions (Murphy et al., 2007). Another study identified a relationship between Stroop task performance and white matter volume in the frontal lobe, but no specific tracts were identified (Takeuchi et al., 2012).

Work conducted to explore the relationship between specific white matter pathways and performance of the Stroop task have to date produced mixed results. Several have identified the cingulum and anterior sections of the corpus callosum to be significantly associated with interference control in discrete groups of young, middle-aged or older adults from healthy and patient populations (Bettcher et al., 2016; Metzler-Baddeley et al., 2012; Mu, Chen, et al., 2018; Takei et al., 2009) (Bettcher et al., 2016; Mu et al., 2018; Takei et al., 2009;). A smaller number of studies have identified other tracts – i.e. the internal and/or the external capsule (Wolf et al., 2014; Zhang et al., 2014) as also relevant to selective attention.

It should also be noted that other studies, however, have not been able to find the same tract-task associations. (Hirsiger et al., 2016) explored the relationship between cingulum

microstructure, functional connectivity and cognitive changes with age. 201 older adults were recruited for the study. They found that despite a significant relationship between structural connectivity and age they did not observe a significant relationship between cingulum microstructure and cognitive function in older adults. In a subsequent study, neither did they find a significant relationship between larger regions of white matter (frontal lobe) and Stroop performance in healthy older adults (Hirsiger et al., 2017). A similar study using multimodal imaging techniques including DTI and resting state fMRI looked to identify neural correlates potentially acting as mediators of age related decline across three different composite functions: processing speed, executive function and memory in a data set of healthy adults aged between 19 and 79 years of age (Madden et al., 2017a). The Stroop task was included in the executive function and processing speed composite scores. What they found was that resting state functional connectivity of sensory motor networks (motor, visual and ganglia/thalamic regions) were shown to be a significant mediator of the age-related decline of executive function, but not specific white matter pathways. White matter tracts included in the analysis were the arcuate / SLF III, the ILF, optic radiation, cortico-spinal tract and genu and splenium of corpus callosum. Of note, did not include the cingulum in this study.

1.7.1.4 Research question

From the literature discussed above, it appears that there are insufficient studies reporting, let alone replicating findings of white matter pathways to be able to reliably determine which ones definitively play a significant role in selective attention. However, what we do know is that the anterior cingulate and DLPFC have been reported regularly as being associated with this cognitive function in functional neuroimaging studies, with the greater weight of evidence focusing on the anterior cingulate. There are also preliminary results indicating the cingulum, the tract underpinning the anterior cingulate may be of relevance. We therefore propose to look in more detail at this tract in the first instance.

Of the studies previously described, correlations between cingulum microstructure have focused either on patient groups or discrete age ranges in healthy adults (Bettcher et al., 2016; Mu et al., 2018; Takei et al., 2009). There is still therefore a need to a) replicate findings of an association between cingulum microstructure and selective attention and b) to test whether changes to cingulum microstructure plays a role in changes to selective attention across the adult lifespan.

Following outcomes from this first stage of analysis, an examination of other pathways associated with the DLPFC (for example, the anterior segments of the corpus callosum) is recommended.

Cingulum and attention: The cingulum, as described in more detail in section 2.1.1 connects the anterior and posterior cingulate cortex to medial parietal, occipital and temporal lobe cortices, i.e. it transfers information from the frontal lobe to other more posterior and inferior regions of the brain. As previously mentioned, activation of the medial frontal lobe (anterior cingulate) has been observed when conducting Stroop tasks in PET (Bench et al., 1993; Carter et al., 1995) and functional neuroimaging studies (Floden, Vallesi, & Stuss, 2011; Rizk et al., 2017). In their study identifying two differing networks of activation during either *reasoning* focused or *working memory* focused tasks, (Hampshire et al., 2012) found that function of selective attention correlated more closely with the reasoning network which included the dorsal region of the anterior cingulate cortex. White matter underpinning not only frontal but also parietal and temporal regions of the cingulate has also been identified as relevant to selective attention (Murphy et al., 2007). Studies delineating the cingulum tract specifically have also identified correlations between its microstructure and performance of the Stroop task in patient groups (Mu, Chen, et al., 2018; Takei et al., 2009).

Cingulum, attention and ageing: To our knowledge, no study has yet considered what role cingulum microstructure may play in supporting selective attention (interference control) across the full healthy adult lifespan. To replicate and extend our knowledge of the potential role this tract plays in selective attention and cognitive ageing, the following research question is therefore proposed:

Does microstructure of the cingulum play a mediatory role in the age-related decline in selective attention in healthy adults?

1.7.1.5 Hypothesis and statistical model

To answer this question, a null hypothesis is defined as 'We predict that cingulum HMOA will present no significant mediation effect on the relationship between age and selective attention in healthy adults.'

The *alternative* hypothesis would thus be: 'We predict that a reduction in cingulum HMOA will play a significant mediatory role in the decline of selective attention with age.'

To test this hypothesis, mediation analysis will be run to obtain information regarding significance of all four paths (a, b, c & c') as per (Baron & Kenny, 1986) and bootstrap (BCa confidence interval) methods will be applied to additionally calculate the indirect effect of the mediator variable (cingulum HMOA) on the relationship between age and selective attention performance. Two sets of analysis will be run, one for each tract per hemisphere (left and right cingulum).

For the mediation analysis to be applied, the following assumptions need to be met:

- A significant relationship between age (predictor variable) and selective attention (outcome variable), (path c, Fig. 2)
- A significant relationship between age (predictor variable) and cingulum HMOA (mediator variable) (path a, Fig. 2)
- A significant relationship between cingulum HMOA (mediator variable) and selective attention (outcome variable), (path b, Fig. 2)

Therefore, the following preliminary tests will be run:

- A regression test to assess the relationship between age and performance of selective attention
- A regression test to assess the relationship between age and cingulum HMOA (tracts from the left and right hemisphere)
- A correlation analysis to assess whether there is a significant relationship between cingulum HMOA (left and right) and performance of selective attention.

If these pre-requisites are met, then the tract (left and/or right cingulum) will be a candidate for mediation analysis. To be able to state that the null hypothesis is *unlikely* (i.e. the probability of no effect being observed is less than 0.05%) and that the alternative hypothesis could then be supported, we would need to demonstrate:

1) that the direct relationship (path c) between age (predictor) and selective attention (outcome) is stronger than the indirect relationship (including the mediator variable) between age and selective attention (path c', Fig. 2).
2) that cingulum HMOA produces a significant indirect effect on the *negative* relationship between age and spatial working memory performance.

This model is explained in more detail in the methods chapter, section 3.6. The number of tests used to answer this research question is still reasonably small, so no correction for multiple comparisons will be applied in this instance.

1.7.2 Ageing, white matter and spatial working memory

1.7.2.1 Spatial working memory

Working memory is the ability to retain or even manipulate several small pieces of information in the mind for a short period of time. In their review (Smith & Jonides, 1997) describe working memory as 'considered critical because it presumably serves as a mental blackboard for computations used in higher-level processes such as reasoning, problem solving, and language understanding'.

1.7.2.2 Measurement of spatial working memory

The Corsi Block Tapping task developed in the 1970's (Corsi, 1972a) has been frequently used in studies to measure spatial working memory in healthy and patient groups. Using a board with 9 cubes attached to it in an asymmetrical pattern (Fig. 1b), an instructor taps on a small number of the cubes in a set sequence. The participant is then required to tap the cubes in the same order as the instructor. The ability of an individual to remember the location of specific objects in space in a given order tends to be limited to an average of 6.2 locations (± 1.3) in healthy adults (mean 31.2 years of age < 3.2). This maximum number or 'span' declines slightly with age to an average of 4.42 <0.89 after the age of 80 (Monaco, Costa, & Caltagirone, 2013). Computerized versions of this task, such as the one designed by (Hampshire, 2015) are now also available to use. For more details of this task see methods chapter, section 3.3.4.

1.7.2.3 Neural correlates of spatial working memory

The frontal, parietal, occipital and medial temporal lobes have all been identified as playing an a role in spatial working memory through PET and fMRI studies (Cocozza et al., 2018; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Jonides et al., 1993; Owen, Evans, & Petrides, 1996; van Asselen et al., 2006). An alternative method using transcranial direct stimulation to the DLPFC demonstrated that activation of this regions resulted in completion of the Corsi Block Tapping task under conditions where the participants were required to inhibit distracting stimuli (Wu et al., 2017).

The spatial working memory task used in this study is the same as one of the tasks that most closely aligned with the working memory network identified by (Hampshire et al., 2012) which

included the superior frontal sulcus, frontal operculum and insula, supplementary motor area (SMA) and anterior cingulate cortex. The cingulum connects the anterior cingulate with medial parietal, occipital and temporal lobes. The superior longitudinal fasciculus system connects regions such as the SMA, superior frontal sulcus and frontal operculum with the parietal lobe. The IFOF connects polar and more ventrolateral regions of the frontal lobe with primarily the occipital lobe (with minor branching to parietal and temporal regions).

Other studies have observed the relationship between the anatomical location of lesions in patient cohorts with performance of visuospatial working memory, measured using the Corsi Block Tapping task. Using voxel-based morphometry they have found that damage in posterior parietal and occipital cortical regions and the posterior segment of the arcuate was associated with low memory span using the Corsi task. Subsequent analysis using tract wise lesion deficit analysis revealed associations between disconnections in the arcuate, IFL, IFOF, SLF system and reduced task performance (Chechlacz, Rotshtein, & Humphreys, 2014). In a later study white matter density of the IFOF and SLF system in the right hemisphere was found to be associated with reduced short term memory ability (Humphreys & Chechlacz, 2015).

Recent publications from a study exploring the impact of working memory training found an increased efficiency within frontoparietal networks after working memory training on healthy subjects (Caeyenberghs, Metzler-Baddeley, Foley, & Jones, 2016) and a significant relationship between increased working memory capacity and changes to a component weighted heavily towards microstructure of the SLF and cingulum (Metzler-Baddeley et al., 2017).

In terms of which neural correlates are involved in the changes to working memory performance with age, functional neuroimaging methods have been used to observe that regions within the prefrontal cortex are activated differently in older adults compared to young adults (Bauer, Sammer, & Toepper, 2015; Toepper et al., 2014) when conducting spatial working memory tasks. Using a spatial working memory task and TBSS (Oberlin et al., 2016) found white matter FA of anterior corona radiata, internal capsule, fornix, cingulum and corpus callosum mediated the relationship between increased aerobic fitness and spatial working memory performance in older adults. However, beyond the work from this study, there is little in the literature seems to confirm

how specific white matter pathways associated with these cortical regions may influence changes to spatial working memory performance with age.

1.7.2.4 Research question

From the functional neuroimaging studies already mentioned a broad range of cortical regions are involved in working memory. More recent work examining white matter pathways have identified a reasonably large number of tracts of interest associated with these cortical regions; - the corpus callosum, fornix, internal capsule, anterior corona radiata, cingulum, ILF, IFOF, and SLF system. Work exploring white matter pathways has been patchy in that it either focuses on patient groups, or a single age range – (young or older) of healthy adults. To our knowledge, there has not been a study investigating changes in white matter pathways associated with spatial working memory across the whole adult lifespan. When combining evidence from functional and structural studies together, tracts that seem to be most frequently mentioned are those connecting the frontal lobe to other brain regions - such as the SLF system, the internal capsule, IFOF and cingulum. It was not possible at the time of the study to include projection pathways in the analysis, however the cingulum, IFOF and SLF could be further examined.

The cingulum, IFOF and SLF and spatial working memory:

The cingulum as already described in section 1.7.1.4 and in more detail in section 2.1.1 is a white matter pathway travelling just below the cingulate cortex through from the medial frontal to medial parietal structures before arching back through the occipital cortex into the medial temporal lobe. In their paper (Hampshire et al., 2012) reported the anterior cingulate cortex as one of the key cortical domains associated with a working memory component, highlighting the relevance of the anterior segments of the cingulum. A study by (Oberlin et al., 2016) draws attention to the *left* cingulum in mediating the relationship between cardiovascular fitness and spatial working memory performance in a group of older adults. In addition, the *left parahippocampal* regions of the cingulum has been identified as relevant to working memory capacity by (Metzler-Baddeley et al., 2017) in a group of healthy young adults.

The IFOF is one of the largest association tracts in the brain and travels from the medial and lateral orbitofrontal and ventrolateral regions of the frontal lobe to the inferior lateral aspect of the occipital lobe There have also been observations of minor branching to the parietal and temporal

lobes. (see section 2.5.1 for more detail). The orbito frontal cortex is thought to in part be involved in top down modulation of some attentional processes. The inferior lateral regions of the occipital lobes have been associated with functions such as recognition of colours, shapes and spaces, spatial attention and visual memory retrieval.

The SLF system is a set of three shorter pathways in each hemisphere that connect primarily the lateral frontal with lateral parietal regions. Frontal termination points connect to some medial aspects of the SMA (SLFI), posterior regions of the dorsolateral (SLFI and SLFII) and ventrolateral (SLFII and SLFIII) regions of the frontal lobe. Some of the functions associated with these regions include motor planning, executive function and speech. Parietal termination points of the SLF system are found in the precuneus, superior parietal lobe, anterior intraparietal sulcus, angular gyrus and inferior parietal lobe. The parietal lobe (regions posterior to the primary somatosensory cortex) has previously been associated with language processing (Catani, Jones, & ffytche, 2005), visually guided movements (Budisavljevic, Dell'Acqua, Zanatto, et al., 2017; Howells et al., 2018), spatial awareness, attention (Chechlacz, Mantini, Gillebert, & Humphreys, 2015; Corbetta, Miezin, Shulman, & Petersen, 1993; Thiebaut de Schotten, Dell'Acqua, et al., 2011) and working memory (Chechlacz et al., 2014). (More detail regarding the anatomical connections of these pathways are described in section 2.6.1).

Both the IFOF and SLF system are reported to be associated with impaired visual working memory or short term memory in patient (Chechlacz et al., 2014) and healthy (Chechlacz, Gillebert, Vangkilde, Petersen, & Humphreys, 2015) groups. One perspective of why this may be the case is that these tracts may be primarily involved in visuospatial attention, a supporting cognitive process required in order to sustain focus during the completion of the task. (It should be noted that visuospatial attention is a slightly different facet of attention to selective attention described in the previous section 1.7.1). Indeed, both the IFOF and segments of the SLF have been associated with visuospatial processing/attention in previous studies (Thiebaut de Schotten, Dell'Acqua, et al., 2011; Urbanski et al., 2008). Lastly, in a meta-analysis conducted by (Parlatini et al., 2017) the SLF system was associated with measures of attention and working memory.

The cingulum, IFOF and SLF, spatial working memory and ageing:

As mentioned earlier, while there are studies reporting on associations between these tracts and spatial working memory in participant groups with discrete age ranges (e.g. young adults or older adults), to our knowledge no study has considered what role all these tracts may play in changes to spatial working memory along the continuum of the full adult lifespan. Therefore, the following research question was proposed:

Does microstructure of the cingulum, inferior fronto-occipital fasciculus and superior longitudinal fasciculus system play a mediatory role in the age-related decline in spatial working memory in healthy adults?

1.7.2.5 Hypothesis and statistical model

To answer this question, a null hypothesis is defined as follows: 'We predict that changes to microstructure of some or all of the following tracts (the cingulum, IFOF and SLF system), will not present a significant mediation effect on the negative relationship between age and spatial working memory in healthy adults.'

The alternative hypothesis would thus be: 'We predict that a reduction in HMOA of some or all of the following tracts (the cingulum, IFOF and SLF system) will play a significant mediatory role in the decline of spatial working memory with age in healthy adults.'

The same preliminary (regression and correlation) and mediation tests will be applied as previously described in section 1.7.2.5. Due to the larger number of tracts included in this hypothesis, the appropriate Bonferroni correction for multiple comparisons will be made for all pre-requisite tests run. A detailed description of these tests can be found in section 3.6

Only tracts that exhibit significant age/HMOA relationships and tract performance/HMOA relationships will be identified as candidate tracts for mediation analysis. Depending on the results of the preliminary tests, up to 10 separate mediation analysis *could* be run (as described in section 1.5, 1.7.1.5 and 3.6). However, corrections for multiple comparisons will have already been applied to the prerequisite tests and due to limited guidance in the literature regarding best practice for multiple mediation models, no further corrections will be applied to at this stage.

1.7.3 Ageing, white matter and planning

1.7.3.1 Planning

The ability to plan is essential for goal directed behaviour. It involves the identification and sequencing of various steps or activities in the correct order to enable transition from a current situation to a goal situation. For example, one might need to check and plan to take various modes of transport, in the right order (a bus, a tube, walking) to ensure successful travel from home (current situation) to a new restaurant in town (goal situation). (Hayes-Roth & Hayes-Roth, 1979) summarize the planning process as 'the predetermination of a course of action aimed at achieving some goal.' When an individual becomes unable to plan it can impact their day to day lives dramatically. A poignant real-life example of this was described by Penfield in 1935. After his sister had recovered from right frontal lobe surgery to remove a tumour, he observed that she struggled to prepare a meal for friends effectively, despite this being something she was particularly good at before her injury. She could still cook individual items separately but could not organise their sequence correctly (Penfield & Evans, 1935).

1.7.3.2 Measurement of planning

The Tower of London task was developed by Shallice in 1982 in order to measure frontal lobe function in patients with frontal and posterior lesions (Shallice, 1982). The Tower of London task consists of three rods inserted into a horizontal base equidistant to one another. The rods are progressively shorter from left to right. 3 balls are each a different colour and are placed onto the rods in an apparently random pattern at the start of the test. The participant is asked to move the balls into a goal pattern in the minimum number of moves, but they are only allowed to move one ball at a time (Fig. 1c).

The Tower of London task has been validated as a sensitive measure of planning and problem-solving abilities (Unterrainer et al., 2004). Tower of London performance is also thought to be associated with fluid intelligence (Duncan, Emslie, Williams, Johnson, & Freer, 1996), inhibition, and attention. Computerized versions of this task, such as the one designed by (Hampshire, 2015) are now also available to use. For more details of this task see Methods chapter, section 3.34.

1.7.3.3 Neural correlates of planning

As previously mentioned, lesion studies have identified the frontal lobe as essential for planning function (Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Stuss & Benson , 1984). This has been corroborated by data collated from fMRI, SPECT and PET methods in healthy subjects and patient groups (Baker et al., 1996; Dagher, Owen, Boecker, & Brooks, 1999; Lazeron et al., 2000; Liemburg et al., 2015; Lorenz et al., 2018; Owen et al., 1990). In addition, a meta-analysis of the use and validity of the Tower of London task supported the involvement of the frontal lobes (Sullivan, Riccio, & Castillo, 2009).

Additional cortical and subcortical regions activated when participants are performing the Tower of London task are the parietal lobe and striatum, with some references to the cingulate, SMA and amygdala (Jones, Chase, & Fournier, 2016; Rive, Koeter, Veltman, Schene, & Ruhe, 2016; Trujillo et al., 2015; van den Heuvel et al., 2003).

The spatial planning task in this study most closely aligns with the reasoning network identified by (Hampshire et al., 2012) which included the inferior frontal sulcus, inferior parietal cortex, SMA and dorsal anterior cingulate. This would imply involvement of ventrally based fronto-parietal connections (i.e. the SLFII and SLFIII and potentially some branches of the IFOF). However in a more recent study utilizing neuroadaptive Bayesian optimization techniques (Lorenz et al., 2018) found that the activation patterns when conducting the Tower of London task aligned more with dorsal fronto-parietal networks (potentially implicating SLFI and SLFII). Both these fMRI studies involved reasonably small numbers (16 - 31) of healthy young adult participants.

Less research has been conducted examining specific white matter pathways connecting cortical or sub cortical regions. One study identified associations between fractional anisotropy (FA) and apparent diffusion coefficient (ADC) of the genu of the corpus callosum and fornix as potentially involved in changes to planning performance (Kaller et al., 2015) in a group of young healthy adults. Another study focusing on cognitive deficits in patients with Parkinson's Disease found an association between performance on the Tower of London task and increased mean diffusivity (MD) in the cingulum, fronto-parietal segment of the arcuate (also sometimes aligned with the SLF III), IFOF and ILF in Tower of London task performance (Duncan et al., 2016). In another study, one research group found that comparing healthy older adults with those who suffered

MCI, the number of errors produced when performing the Tower of London task by the MCI participants correlated with mean diffusivity in the left and right anterior cingulum (Metzler Baddeley, 2012).

1.7.3.4 Research question

To summarize, from lesion and functional neuroimaging studies a broad range of cortical and subcortical regions have been associated with planning, with primary regions of interest being within the frontal and parietal lobes and some sub cortical structures. Despite the prominence of fronto-parietal regions in the literature however, no studies to date have explicitly investigated what the role SLF system (a set of pathways directly connecting these two regions together (Thiebaut de Schotten, Dell'Acqua, et al., 2011)) plays in planning performance declines over the adult lifespan. The aim of this third research question is primarily to investigate changes across the lifespan of the SLF system and what role this plays in age related planning deficits. It is also important to acknowledge the involvement of supporting processes such as attention and working memory required for planning function. For the previous two research questions, the cingulum and IFOF were included as tracts of interest for these cognitive functions as previously described. These tracts will also be included in this third research question proposed as follows:

Does microstructure of the cingulum, inferior fronto-occipital fasciculus and superior longitudinal fasciculus system play a mediatory role in the age-related decline in planning ability in healthy adults?

1.7.3.5 Hypothesis and statistical model

To answer this question, a null hypothesis is defined as follows: 'We predict that changes to microstructure of some or all of the following tracts (the cingulum, IFOF and SLF system), will not present a significant mediation effect on the negative relationship between age and planning ability in healthy adults.' The alternative hypothesis would thus be: We predict that a reduction in HMOA of some or all the following tracts (the cingulum, IFOF and SLF system) will play a significant mediatory role in the decline of planning ability with age in healthy adults. The same approach to test this hypothesis will be applied as that described in sections 1.7.1.5 and 1.7.2.5.

1.8 Exploratory analysis

As previously mentioned, executive function is a complex, age sensitive process. In order to explore the wider role of frontal lobe pathways in executive function, additional tracts and behavioural measures were included in a series of exploratory analysis. Two frontal lobe tracts, the frontal aslant tract and the uncinate were included, alongside the corpus callosum segmented into anterior, central and posterior sections. Two further behavioural measures of executive function (feature match and self-ordered search) and a third task utilising both executive problem-solving processes and episodic memory (paired associates), were also described.

In addition to the functions aligned with the cingulum in the previous sections (1.7.1 – 3), this tract has been associated with tasks measuring executive function such as the trail making task and its damage has been associated with impaired executive function in patient groups. It has also been identified as relevant to cognitive processes such as attention, visuospatial processing, processing speed and memory (more details are provided in section 2.1.2).

The IFOF, in addition to the functions identified in the previous sections has been associated with forms of visuospatial processing which may be pertinent to the feature match task described below (see section 2.5.2 for more details).

The SLF system, aside from the functions previously listed in previous sections, has been associated with forms of visuospatial attention and aligned loosely through its anatomical connections to spatial working memory (as before, more details of SLF system function can be found in section 2.6.2).

The corpus callosum is the largest white matter tract in the brain connecting left and right hemispheres together primarily across the frontal, parietal and occipital lobes, but also to a lesser extent the temporal lobes as well. An anterior to posterior gradient of microstructural decline has been observed in the corpus callosum and this pattern plays a critical role in the ‘First in last out’ ageing hypothesis (Abe et al., 2002; Pfefferbaum et al., 2000). There are also preliminary results indicating its potential involvement in executive function (Bodini et al., 2013; Granberg et al., 2015).

The frontal aslant tract (FAT) is an intralobar tract that connects posterior dorsal and ventral regions of the frontal lobe together. There is some preliminary evidence for its involvement in working memory (Rizio & Diaz, 2016) although it is primarily described as a pathway supporting language function (Catani et al., 2013; Fujii et al., 2015).

The uncinate pathway connects polar, orbital and anterior ventrolateral regions of the frontal lobe to the medial temporal lobe. While previously considered a pathway supporting language and emotional processing, recent research has identified a potential role in attention and working memory processes (Charlton, Barrick, Lawes, Markus, & Morris, 2010; Diao et al., 2015; Singh et al., 2016).

The feature match task measures perception and selective visual attention (Desimone & Duncan, 1995; Moore & Zirnsak, 2017) by requiring an individual to compare between similar sets of features (in the form of two boxes side by side containing simple or complex patterns depending on the level of difficulty of the task) and identifying any differences. This function is thought to involve the cognitive processes of object recognition, and selectivity (the ability to screen out irrelevant information). Previous studies using tasks that require focused attention to detect a particular target have identified the ventrolateral prefrontal cortex (inferior frontal gyrus) as being involved (Hampshire, Thompson, Duncan, & Owen, 2009). In their review (Corbetta & Shulman, 2002) outlined the frontal eye fields, posterior parietal cortex and intraparietal sulcus as being associated with controlling the location of attention.

The self-ordered search task is thought to involve the cognitive processes of planning, inhibitory control and working memory. It was adapted from a task designed by (Collins, Roberts, Dias, Everitt, & Robbins, 1998) for experiments with primates where performance was associated with the prefrontal cortex in marmosets. In a similar task, the subject ordered pointing test, patients with frontal and temporal lobe lesions displayed deficits in performance (Petrides & Milner, 1982). Another study found that frontal lobe lesions were associated with an inefficient search strategy during a spatial working memory task whilst lesions in the medial temporal lobe related to performance of visual and verbal working memory tasks. The researchers suggested the frontal regions are associated with the ‘executive’ search strategy whereas the temporal regions are

associated with mnemonic functions (Owen, Morris, Sahakian, Polkey, & Robbins, 1996). Further lesion studies in humans reported correlations between performance in the multiple-location search task and damage to the hippocampus (Abrahams, Pickering, Polkey, & Morris, 1997; Parslow et al., 2005). Results from a PET study using a spatial monitoring task similar to the spatial search task observed significant activation in the mid DLPFC (BA46, 9) during active monitoring and manipulation of information and the ventrolateral frontal cortex (BA 47) during more simple working memory processes (Owen, Evans, & Petrides, 1996).

The paired associates task primarily measures episodic memory, i.e. an individual's ability to encode the image of an object (for example a table lamp or a plump zebra) and bind or 'associate' these with a specific location to then be able to retrieve the correct location when provided with the object as a cue. It has also been suggested that this task also requires more typically executive processes such as attention and working memory (Moscovitch, 1992). A broad range of cortical regions have been found relevant for this task. The hippocampal and para-hippocampal regions of the medial temporal lobe are thought to be involved in the learning aspects whereas fronto-parietal, occipital and cerebellar regions have also been identified as relevant. Tasks measuring the process of 'paired associate learning' (PAL) come in many shapes and forms. Some use pairs of words and others are visuospatial in format. Both types of tasks show performance decline with age (Naveh-Benjamin, 2000; Old & Naveh-Benjamin, 2008; Witte & Freund, 1976). Performance of these tests are also notably lower in patients with Alzheimer's Disease (Egerhazi, Berecz, Bartok, & Degrell, 2007; Fowler, Saling, Conway, Semple, & Louis, 1997).

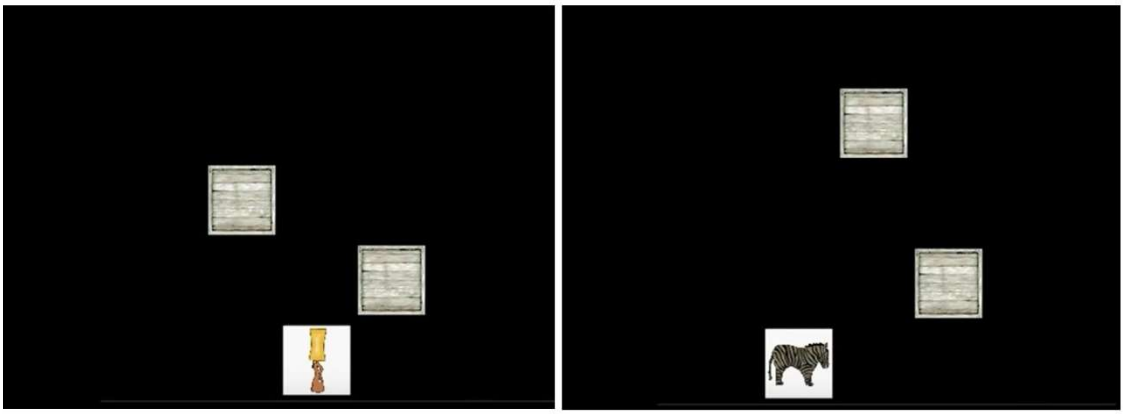


Figure 3 Examples of objects (table lamp or plump zebra) in the Paired Associates task

Descriptive analysis assessing age related declines in task performance and tract microstructure were conducted. Tests to assess correlations between all tracts and all tasks (outside of the original three research questions) were also run. Finally, for appropriate combinations of tracts and tasks, mediation analyses were also conducted.

Chapter 2 White matter tracts of interest

Six association pathways (the 3 segments of the SLF system, cingulum, IFOF and uncinate), one intralobar tract (frontal aslant tract) per hemisphere, and the corpus callosum (segmented) were identified as white matter tracts of interest. All association tracts were chosen due to their origination or termination points (depending on your perspective) in the frontal lobe, a region already described in the literature as both sensitive to changes with age and critical for executive function. The cingulum and SLF system both traverse frontal and parietal lobes and were of greatest interest due to their connection between these regions. The IFOF and uncinate are positioned in more polar/orbital areas of the frontal lobe and connect the occipital (and part of the parietal and temporal lobes) and anterior temporal lobes respectively. The FAT was included due to its location in the posterior frontal lobe although it is primarily known for language and motor function rather than executive function. The segmented corpus callosum was also included in analysis to allow for replication of the anterior-posterior gradient of aging described by (Abe, Aoki, Hayashi, Yamada, Kunimatsu, Mori, Yoshikawa, Okubo, & Ohtomo, 2002b; Pfefferbaum et al., 2000b).

This chapter gives an overview of the current understanding of each of these pathways, their anatomy and functions and highlights any evidence to date presented in favour of their involvement in executive function.

2.1 Cingulum

2.1.1 Anatomy

The cingulum is an association pathway connecting the medial frontal, parietal, occipital and temporal lobes in the shape of an inverse ‘c’.

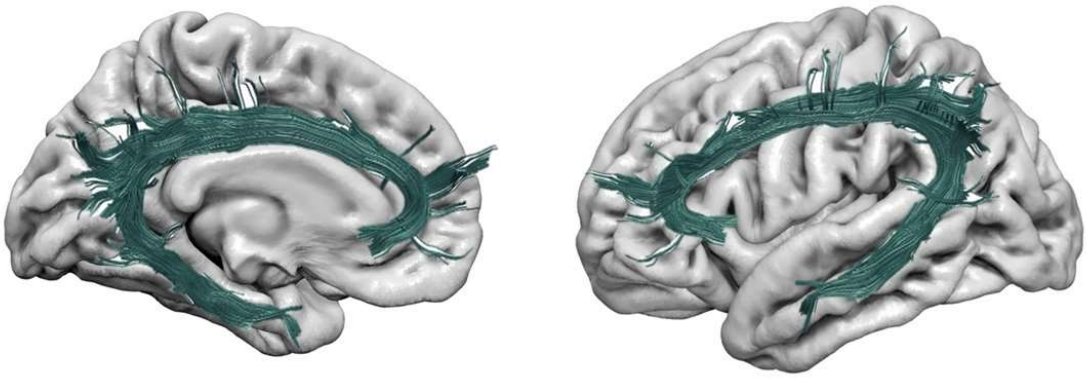


Figure 4 Cingulum

Cingulum fibres in the frontal lobe originate beneath the genu of the corpus callosum. They travel up and over the genu and then back towards the posterior sections of the brain by skimming over the body of the corpus callosum. From there they curve down around the posterior limits of the splenium before changing course once again to advance in an antero-lateral direction into the temporal lobe. The temporal fibres terminate by nestling within the para-hippocampal gyrus. The fibres in this region have been observed to be more diffuse (Mori & Aggarwal, 2014) than in other sections of the tract.

The cingulum also includes shorter ‘U’ shaped fibres that connect neighbouring cortical regions together along the length of its dorsal section (Catani & Thiebaut de Schotten, 2012). The combination of these long and short fibres mean that the cingulum is connected to the medial aspects of the frontal, parietal, occipital and temporal lobes (Fig. 3). However due to the angle thresholds set for pre-processing of imaging data, delineation and metrics of U shape fibres were not possible to extract for this study.

The cingulum is related in terms of proximity, yet separate and distinct in structure from the grey matter of the cingulate gyrus. Currently, more is known about the function of the cingulate gyrus than the cingulum. An overview of the cingulate gyrus can be found in section 2.1.2.9.

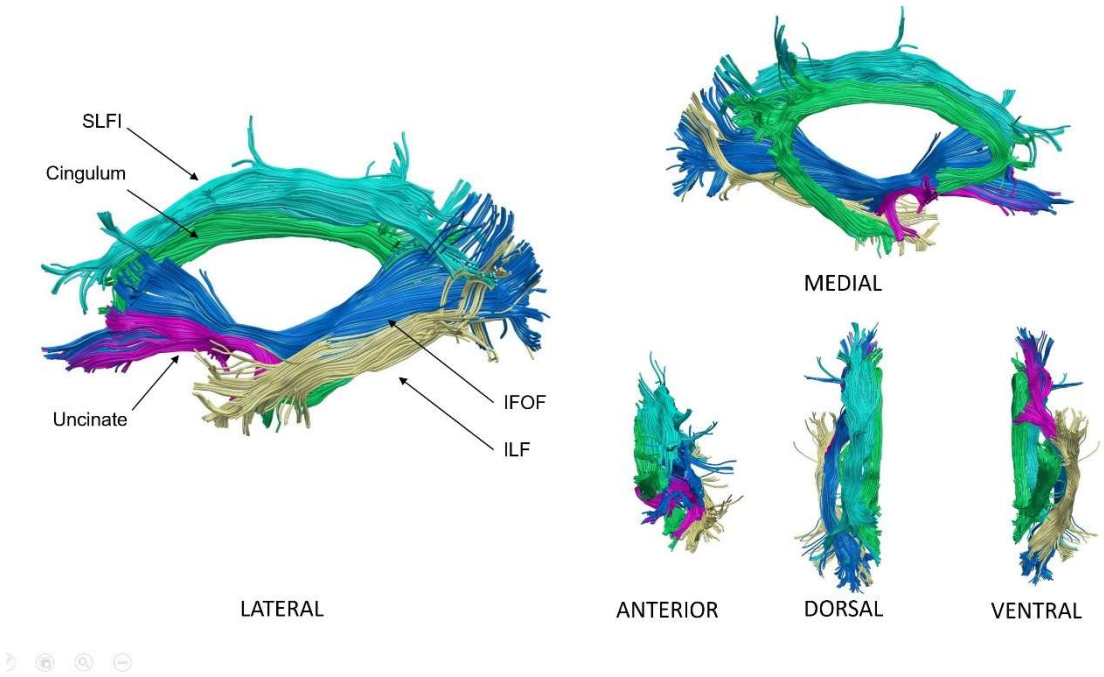


Figure 5 Neighbouring tracts of the cingulum

Neighbouring tracts of the cingulum, in addition to the corpus callosum, are the superior longitudinal fasciculus I (SLFI), which lies dorsally to the antero/dorsal sections of the cingulum; the inferior longitudinal fasciculus (ILF), which travels laterally to the para-hippocampal segment of the cingulum; as does a portion of the fornix (not visualised in Fig. 5). The frontal and occipital termination points of the inferior fronto-occipital fasciculus (IFOF) are proximal to the frontal and occipital fibres of the cingulum. The most anterior temporal fibres of the cingulum terminate medially to the temporal fibres of the uncinate (see Fig 5).

Several different approaches to segmentation of the cingulum have been explored in the literature. The simplest approach has been to divide the cingulum into anterior-dorsal, and posterior-ventral (para-hippocampal) segments (Catani & Thiebaut de Schotten, 2012; Wakana et al., 2007).

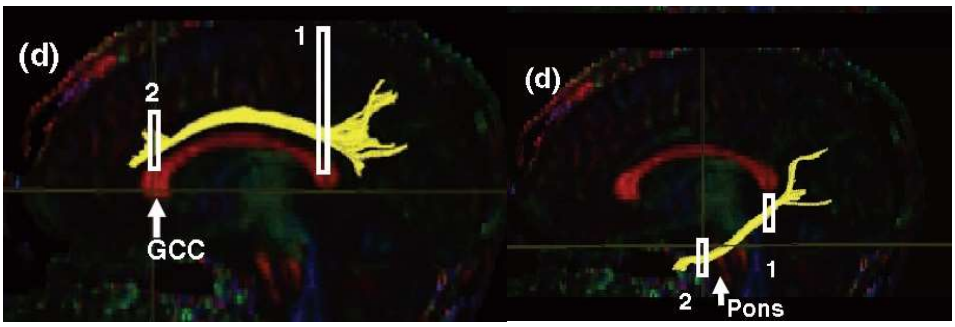


Figure 6 Segmentation of cingulum according to (Wakana, 2007)

Other research groups have divided the cingulum into three (Metzler-Baddeley et al., 2012) or five segments (Jang, Kwon, Lee, Kim, & Seo, 2016a; Wu, Sun, Wang, Wang, & Ou, 2016). For the purposes of this thesis, the cingulum is being examined initially as an entire tract in line with all other association tracts examined.

There are differing reports referring to volumetric asymmetries in the cingulum. In a small group of 10 young adults (mean age 26.1, ± 5.48 years) (Wakana et al., 2007) found the left cingulum to be significantly larger than the right. However, this was not corroborated by a subsequent study (Thiebaut de Schotten, Ffytche, et al., 2011). Reports of microstructural asymmetries are also mixed, although there is perhaps growing evidence for higher FA in the left cingulum (leftward asymmetry) compared to the right, particularly in more anterior (Park et al., 2004; Takao et al., 2011) or mid sections of the cingulum (Huster, Westerhausen, Kreuder, Schweiger, & Wittling, 2009). Counter to this, other studies have found a rightward asymmetry of FA in para-hippocampal sections of the cingulum (Metzler-Baddeley et al., 2012; Wakana et al., 2007).

2.1.2 Function

2.1.2.1 Executive function

Several studies have found performance of various executive function tasks to correlate the cingulum microstructure, although this is primarily observed in patient groups. For example, a study investigating performance in language, attention, executive function, visuospatial processing and memory tasks in a population of older adults who were either healthy or diagnosed with Mild Cognitive Impairment (MCI) found that impaired executive function (measured by the Trail making test, part B) correlated significantly with FA of the anterior and posterior cingulum and the ILF (Kantarci et al., 2011). When using the Tower of London task, one research group

found that comparing healthy older adults with those who suffered MCI the number of errors produced by the MCI participants correlated with mean diffusivity (MD) in the left and right anterior cingulum (Metzler-Baddeley et al., 2012). In addition, a significant association were found between FA predominantly (but not solely) in the left anterior cingulum and performance levels of the Stroop, verbal fluency and digit symbol tasks.

A significant correlation between reduced performance in executive function tasks in groups of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADSIL) and Coronary Artery Disease (CAD) patients, were found in MD levels of the left anterior cingulum (O'Sullivan, Barrick, Morris, Clark, & Markus, 2005), and FA levels in the left para-hippocampal cingulum (O'Sullivan et al., 2005; Santiago et al., 2015) respectively. In a different type of participant group, degraded executive performance in a war veterans who suffered mild TBI revealed significant relationships with reduced FA in pre-frontal white matter, the corpus callosum and the cingulum (Sorg et al., 2014).

2.1.2.2 Attention

Scores for the Continuous Performance Test (CPT) measuring attention correlated with FA in the right cingulum (Takahashi et al., 2010) in healthy young adults. Alternatively, in a group of patients diagnosed with Schizophrenia, reduced visual orienting as part of an alternative attentional task correlated significantly with FA of the left cingulum (Nestor et al., 2007). (Bettcher et al., 2016) found significant associations between the cingulum FA with a cognitive component of shifting/ inhibition which included performance measures of the Stroop task.

2.1.2.3 Working memory

Lesions disrupting the path of the cingulum along with fronto-parietal, thalamo cortical and cerebellar white matter regions were observed to correlate with performance of verbal working memory tasks in adult Multiple Sclerosis (MS) patients (Sepulcre et al., 2009). A study by (Oberlin et al., 2016) reported microstructure of the *left* cingulum mediated the relationship between cardiovascular fitness and spatial working memory performance in a group of older adults. In addition, measures of tract microstructure including FA of the *left* parahippocampal regions of the cingulum were associated with changes in working memory capacity (Metzler-Baddeley et al., 2017) in a group of healthy young adults after a cognitive training intervention.

2.1.2.4 Other forms of memory

(Sepulcre et al., 2008) identified relationships between damaged white matter in the cingulum (along with temporal, parieto-temporal, thalamic and internal capsule white matter regions), and declarative verbal memory retrieval in adult MS patients. Reduced scores of episodic memory (and information processing speed) in MS patients compared to controls correlated significantly with the RD and AD of the posterior cingulum (Koenig et al., 2015). Factor scores derived from a group of memory tasks correlated significantly with FA values in the right cingulum (Alexander, Concha, Snyder, Beaulieu, & Gross, 2014) (Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012, 2013) as well as the fornix, ILF, uncinate and SLF.

In contrast, observing a group of unilateral Medial Temporal Lobe (MTL) Epilepsy patients, known to have lower FA levels in the fornix and cingulum, no correlation could be identified with cingulum microstructure (Alexander et al., 2014). Similarly, another study observing cognition and white matter relationships in a population of older adults with evidence of Coronary Artery Disease (CAD) found no correlation between the cingulum (nor other white matter pathways) and memory performance (Santiago et al., 2015).

2.1.2.5 Visuospatial processing

In a group of older adults, a correlation between visuospatial processing (measured by WAIS-R Picture Completion and Block Design tasks) and FA of the posterior cingulum and fornix were found (Kantarci et al., 2011).

2.1.2.6 Processing speed

Factor scores of processing speed performance correlated significantly with apparent diffusion coefficient (ADC) values in the left cingulum (Sasson et al., 2012, 2013) as well as the fornix, ILF and SLF/Arcuate.

2.1.2.7 DMN

The default mode network (DMN) has until recently primarily been investigated using fMRI modalities. Although some studies have started to incorporate white matter metrics into their design. For example (Vidal-Pineiro et al., 2014) found a correlation between lower DMN connectivity and the anterior corpus callosum, cingulum, uncinate and IFOF.

2.1.2.8 Other functions

Lower FA in the ILF and posterior areas of the cingulum correlated with language impairment in a group of older adults (Kantarci et al., 2011).

2.1.2.9 Related functions of the cingulate cortex

It is important to separate out and clarify which research has been done concerning the cingulate gyrus or *cortex* (gray matter) as opposed to the cingulum (white matter pathway). Once such a differentiation has been made, it is possible to start to identify how these regions may be involved in the same, similar or entirely different functions.

The anterior cingulate cortex (ACC) can be divided into two areas; the rostral/ventral (most anterior and inferior) region and the caudal/dorsal (most posterior and superior) region. Functions range from those associated with affect, and mechanisms of the Autonomic Nervous System (ANS) in the ventral/ rostral (anterior) regions to motor and cognitive control in the more caudal (posterior) regions (Bush et al., 2000; Devinsky, Morrell, & Vogt, 1995). The caudal region of ACC may also be involved in monitoring the emotional or affective significance of painful stimuli. The posterior cingulate cortex (PCC) is confined to the medial inferior parietal lobe. It is thought to be part of the DMN (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle, 2015) which is involved in introspective activities such as autobiographic memory, perception of the perspectives of other people and constructing future plans. The parahippocampal regions of the cingulate, in the medial temporal lobe (MTL) where the hippocampus lies has been observed to be involved in functions of spatial memory and navigation (Maguire, Frackowiak, & Frith, 1996; Squire & Zola-Morgan, 1991).

2.1.3 Changes with Age

Changes to the cingulum with age are reported differently across the literature. One research group accessing neuroimaging data from over 400 healthy adult participants observed that the cingulum is the tract that takes the longest to mature, not peaking in FA or reaching lowest MD until over 40 years of age. After this, reduction in FA and increases in MD are gradual (Lebel et al., 2012). However a different group found a significant drop in cingulum FA at a much earlier point - after the age of 20 years (Yoon, Shim, Lee, Shon, & Yang, 2008). In studies where the

cingulum has been segmented, some find significant changes in only one or two segments (not the entire tract) (Jang, Kwon, Lee, Kim, & Seo, 2016b; Sibilia et al., 2017).

It is well documented that in healthy older adults, some aspects of executive function, working memory and episodic memory slightly decline. Changes in cingulum microstructure, among other white matter pathways have been observed and correlated to these cognitive changes in this cohort. For example, a significant relationship between left (anterior/dorsal segment) cingulum FA and performance of Stroop, category fluency and digit symbol substitution tasks has been recorded (Metzler-Baddeley et al., 2012). Likewise, another study found significant correlations between memory, language and executive function decline and the anterior cingulum and other white matter pathways (Kantarci et al., 2011). In a different group of healthy older adults, reduced episodic memory scores correlated with FA in several tracts; the uncinate, ILF and dorsal cingulum (Lockhart et al., 2012). Conversely, although a significant decline in cingulum FA over the adult lifespan was observed, no relationship was found in an older population between executive function or memory function and FA measurements of the cingulum by (Voineskos et al., 2012).

2.2 Corpus Callosum

2.2.1 Anatomy

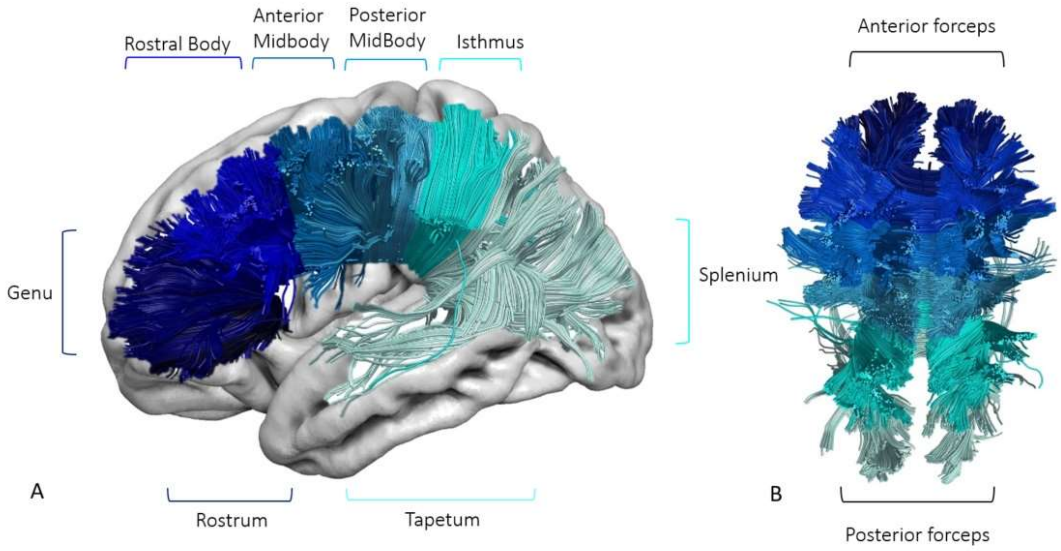


Figure 7 Segmented corpus callosum a) lateral and b) dorsal aspects

The corpus callosum is the largest white matter tract in the brain connecting left and right hemispheres together primarily across the frontal, parietal and occipital lobes, but also to a lesser extent the temporal lobes as well. The most anterior sections are called the anterior forceps or forceps minor and consist of the most orbito - polar regions, the rostrum and genu. The body of the corpus callosum, consisting of the rostral, anterior and posterior mid-body connects the remaining frontal and parietal hemispheres. The most posterior section of the corpus callosum consists of the posterior forceps or forceps major, including the isthmus and splenium that connect the occipital hemispheres. Also stemming from the splenium, a thinner and more diffuse set of fibres called the tapetum extend into the left and right temporal lobes (see Fig. 7 a & b).

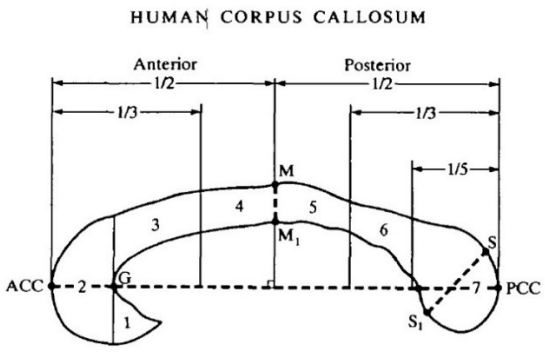


Figure 8 Segmentation of the corpus callosum according to (Witelson, 1989)

One of the most established strategies for segmenting the corpus callosum defined by (Witelson, 1989) is a geometric approach that separates out the midline of the corpus callosum into seven different components. The original analysis was conducted on 50 post-mortem brains. This structured and pragmatic approach has since been adapted for neuroimaging studies. It is this approach that was used for this study. More details can be found in Appendix F.

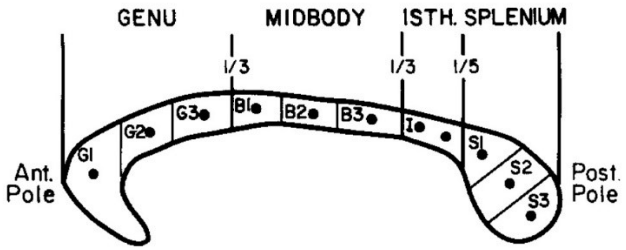


Figure 9 Segmentation of the corpus callosum according to (Aboitiz, 1992)

An alternative segmentation strategy by (Aboitiz, Scheibel, Fisher, & Zaidel, 1992) used histological characteristics along the sagittal midline to divide up the corpus callosum. Of note, the frontal sections of the corpus callosum have a high proportion of thin myelinated fibres whereas towards the middle (somatosensory) region fibres are thicker. Towards the posterior body a higher percentage of thinner fibres resumes but in the most posterior regions (those that connect to visual cortices) the percentage of thick fibres increases again. This study was originally conducted on 20 post-mortem brains (aged 25 – 68 years).

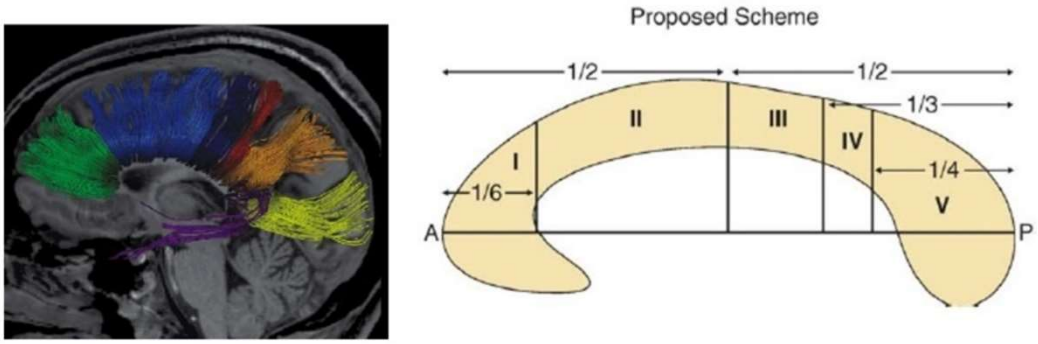


Figure 10 Segmentation of the corpus callosum according to (Hofer, 2006)

A more recent approach based on DTI tractography in based on eight right handed healthy subjects (aged between 21 – 47 years) provides a modified method of segmenting the corpus callosum according to cortical termination points (Hofer & Frahm, 2006).

2.2.2 Function

The primary role of the corpus callosum is thought to be interhemispheric transfer of information. The type of information and therefore functions supported varies across cortical termination points. Over the course of several decades case studies from patients with sectioned corpus callosum have been observed to suffer from a variety of information transfer deficits. These have ranged from motor and perception dysfunctions to more complex language or executive dysfunction (Gazzaniga, 2005). Below I have provided a brief summary of a series of different studies that provide additional evidence to illustrate the great range of functions thought to be supported by the corpus callosum (in an anterior to posterior order).

2.2.2.1 Impulsivity and Executive Function

Increased impulsivity was correlated with FA of prefrontal (**genu** and **rostral body**) segments of the corpus callosum in 18 participants (mean age 33.1 ± 8.7 years) dependent on cocaine compared to 18 healthy controls (mean age 30.3 ± 7.7 years) (Moeller et al., 2005).

In a longitudinal study lasting 17 years, a group of 23 patients (mean age 57 years) suffering from Multiple Sclerosis (MS) were assessed for cognitive decline measuring processing speed, verbal

fluency, verbal learning, visuospatial function, attention, planning and working. A significant positive correlation was observed between whole corpus callosum volume and executive function performance (Granberg et al., 2014). In a group of 25 patients with MS (mean age, ~44 years) compared to age matched controls (aged between 30 – 65 years), decreased FA across the whole corpus callosum correlated with impaired verbal memory, attention, processing speed and executive function (Bodini et al., 2013).

2.2.2.2 Working memory

The extent of working memory recovery in 24 adult patients (aged between 17 – 65 years) after epilepsy resection surgery related to the pre-surgical size of the mid-sagittal area of the corpus callosum (Blackmon et al., 2015). In particular it was the volume of the more posterior sections as divided by (Witelson, 1989) that demonstrated an independent significant relationship with working memory improvement post-surgery.

2.2.2.3 Visuospatial processing

In a recent study, 44 healthy young adults (mean age 21.7 ± 3.4) conducted the Vandenberg mental rotation test to measure visuospatial function. Using a segmentation approach based on (Witelson, 1989), task performance was significantly associated with the volume of the rostrum and anterior midbody (but not the genu or rostral body) of the corpus callosum (Newman, 2016).

2.2.2.4 Language

In 74 healthy subjects (mean age 31 years) performance in two fMRI language tasks was compared to corpus callosum volume on the midsagittal line. Subjects who had greater left lateralized functional activations during these language tasks in the inferior frontal and posterior temporal regions also had a larger volume of the corpus callosum (Josse, Seghier, Kherif, & Price, 2008).

2.2.2.5 Motor and Sensory function

In 18 healthy subjects (mean age 22.3 ± 3.6 years) successful learning of a new bi-manual motor task correlated significantly with FA of the anterior segments of the corpus callosum (Sisti et al., 2012) as opposed to the more posterior segments connecting the primary motor cortices.

Cutting the corpus callosum can impact transfer of sensory and motor information in the hands. In a study of two specific patients post-surgery (Gazzaniga, Bogen, & Sperry, 1967) found that transfer of information in the form of an instruction received by the left hemisphere (e.g. via the left visual field) to the right primary motor cortex, resulted in impeded movement of the left arm and hand, particularly in the distal hand muscles.

In an older population comparing 18 stroke patients (mean age 54.4 ±14.3 years) and 12 healthy controls (mean age 62.5 ± 7.9 years) motor function was measured by an fMRI finger tapping task. Patients demonstrated a more bilateral motor cortex activation during the task. Furthermore, FA of the middle and posterior sections of the corpus callosum, and the ipsilesional cortico spinal tract (CST) correlated significantly with the lateralization index of the finger tapping task (Wang et al., 2012).

Comparing performance of three patients with fully sectioned corpus callosum and patients with only a partially sectioned corpus callosum (aged between 24 – 38 years) with 20 aged matched healthy controls conducting tactile tasks (Fabri et al., 2005) found that the posterior sections of the corpus callosum were required in order to complete the tasks as successfully as healthy controls.

2.2.2.6 Vision

Two separate case studies have illustrated that damage to the splenium can result in dysfunction of interhemispheric transfer of visual information (Le et al., 2005; Molko et al., 2002).

2.2.3 Changes with age

FA decreased with age in the genu rather than the splenium of the corpus callosum in a group of 31 adults (23 – 76 years of age) (Pfefferbaum et al., 2000). In another study of 50 healthy adults (21 – 69 years, mean age 44.8 ± 14.0 years) a similar relationship between age and FA of the genu was found (Abe et al., 2002). The observation that more anterior white matter seemed to have greater sensitivity to age proved instrumental in the development of the Frontal Cognitive Aging Hypothesis. A steeper decline in FA has also been observed in a large study of healthy children and adults aged between 5 and 59 years in the more anterior compared to posterior segments of the corpus callosum. Although it is worth noting, the orbital frontal segment of the corpus callosum did not share this trajectory, and the study was limited in that it did not include adults over the age of 60 years (Lebel, Caverhill-Godkewitsch, & Beaulieu, 2010).

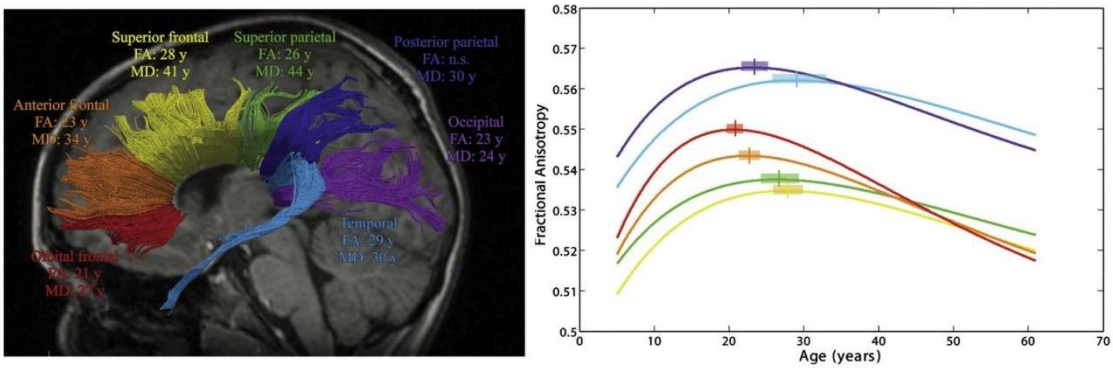


Figure 11 Segmentation of the corpus callosum according to (Lebel 2010)

Other age related patterns of change have been observed as follows: In a longitudinal study assessing 20 healthy adults, 10 young adults (aged between 22 and 40 years) and 10 older adults (aged between 65 and 79 years) (Sullivan, Rohlfing, & Pfefferbaum, 2010a) found that the lateral/distal sections of the corpus callosum were more sensitive to age related changes compared to the central mid region. They did not find significant changes within group changes across the two-year period but did confirm significant differences between groups as expected.

A decline in volume has been associated with motor deficits and poorer MMSE performance in older individuals (Bhadelia et al., 2009; Ryberg et al., 2011, 2007; Yamauchi, Fukuyama, & Shio, 2000). In a group of 170 older adults ranging from healthy to a diagnosis of probable AD, impairment in executive function correlated with corpus callosum atrophy (Meguro et al., 2003). In a dementia cohort earlier atrophy in the posterior sections of the corpus callosum was associated with faster disease progression (Frederiksen, 2013).

(Madden et al., 2009) reported a mediation effect of FA in the genu of the corpus callosum and lateral sections of splenium fibres in the right hemisphere on changes in task switching performance with age in a group of 20 young adults (aged between 18 – 27 years) and 20 older adults (aged between 60 – 85 years).

2.3 Frontal Aslant Tract

2.3.1 Anatomy

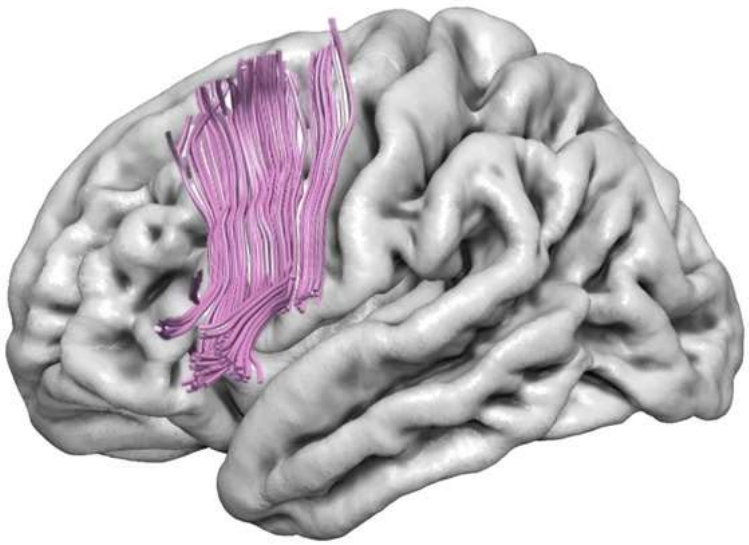


Figure 12 Frontal Aslant Tract

The frontal aslant tract (FAT) travels laterally and ventrally from the posterior section of the superior frontal gyrus (SFg), (i.e. the lateral aspect of the Pre-SMA and anterior sections of the SMA), towards the posterior inferior frontal gyrus (IFg) (i.e. the pars triangularis and pars opercularis). It is a short band of fibres that dip from their most cortical terminations, travelling at a slant beneath the middle frontal gyrus to then resurface in the frontal operculum. It is worth noting that the FAT has also been described as being associated with smaller U shaped fibres that connect the SFg to the Medial Frontal Gyrus (MFg) and the MFg to the IFg (Catani et al., 2012) However, these u shaped fibres have not been included within the scope of the current study.

Whilst acknowledging previous studies alluding to some sort of relationship between the superior frontal gyrus and broca's area, it was (Kinoshita et al., 2012) who claimed to be the first to describe in more anatomical detail a pathway connecting these regions. In 2012 using post-mortem dissection of eight hemispheres and DTI analysis of 53 right-handed patients (mean age 55.1 ±13 years) they described a tract connecting the posterior superior frontal gyrus (BA6) to Broca's area (BA44/45). This group hypothesised a language production role for this pathway but did not provide experimental data to support it at the time. (Catani et al., 2013) subsequently named this pathway the frontal aslant tract and explored in more detail potential functions associated with it.

Other studies have also described the FAT in either post mortem brains or in vivo brains during surgery. (Koutsarnakis et al., 2017; Ookawa et al., 2017).

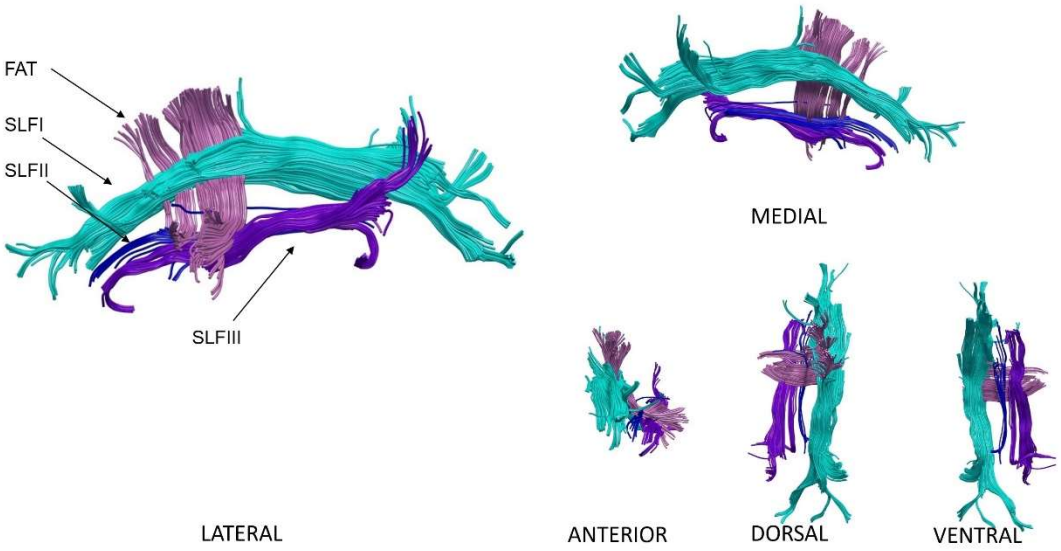


Figure 13 Neighbouring tracts of the FAT

The FAT is proximal to several different types of pathways (Fig 13). A study comparing post mortem dissections with DTI data from the Human Connectome Project describes the FAT as sitting posterior to the fronto-striatal pathway (not included in Fig 13); There could be some U shaped fibres reaching lateral to some terminations from the cingulum at the point of the medial SMA/Pre-SMA although this is not certain (not included in Fig 13); The FAT runs in a direction transverse to the fibres of the SLFI, II and III (Bozkurt et al., 2016).

2.3.1.1 Lateralization

In right handed subjects (Kinoshita et al., 2012) found significant differences between the superior and inferior widths of the FAT. i.e. the width of the FAT at the superior frontal gyrus was 33.8 ± 14.4mm on the left compared to 27.6 ± 17.2 on the right, and the width in the inferior frontal gyrus was 21.5 ±10.00mm in the left compared to 17.6 ±1.6mm in the right.

2.3.2 Function

2.3.2.1 Language

Investigating language impairments in 35 patients with Primary Progressive Aphasia (PPA) compared to 29 controls subjects (mean age 63.2 ±8.3 years for patients, 62.4 ± 6 years for controls), (Catani et al., 2013) suggested damage to the FAT was significantly associated with impaired verbal fluency performance. In a group of 31 post stroke patients (mean age 68.21 years) suffering from impairments with speech fluency, correlations with the arcuate and FAT were found (Halai, Woollams, & Ralph, 2016). Another study describes speech initiation and spontaneity and its relationship with the left FAT (Fujii et al., 2015) in a group of five patients (aged 40 – 54 years) who had glioma's in the left frontal lobe. This was supported by another intraoperative study from (Kinoshita et al., 2015) examining 19 patients (mean age 36 years). Another surgical team looked at the role of the FAT in stuttering in 8 patients (mean age 34.7 ±7.9 years) and found that the cortical regions stimulated to cause intraoperative stuttering were those that matched the cortical terminations of the FAT pathway (Kemerdere et al., 2016). In 15 individuals with persistent developmental stuttering (mean age 32 years (19-52 years), the left FAT and behavioural measures of speech fluency correlated (Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016). A single case study of a 30-year-old woman (right-handed) observed that during surgery, stimulation of the FAT resulted in speech arrest with speech resuming when stimulation ceased (Vassal, Boutet, Lemaire, & Nuti, 2014). Similarly, another case study on surgery of a 25 year old man observed damage to the FAT and arcuate during surgery resulted in temporary impairment of orofacial musculature (Martino, de Lucas, Ibanez-Plagaro, Valle-Folgueral, & Vazquez-Barquero, 2012). Another case study of a 39 year old right-handed woman, observed a relationship between the left FAT and 'lexical retrieval' (Sierpowska et al., 2015).

2.3.2.2 Working memory

In examining four neuropsychological components identified from PCA; language, processing speed, episodic memory and working memory, (Rizio & Diaz, 2016) observed a significant relationship between FA of the FAT and SLF/Arcuate and working memory performance in 25 older adults (59 – 78 years, M= 66.97). No similar relationship however was observed in the younger adult group.

2.3.2.3 Motor function

A recent paper (Budisavljevic, Dell'Acqua, Djordjilovic, et al., 2017) has described an association between microstructure of the FAT and aspects of fine motor control of the hands in 32 right handed healthy young adults (mean age 24.6, ± 2.7 years).

2.3.3 Changes with age

At present, most research examining the FAT in older adults has been conducted on a small number of patients, or postmortem work or healthy young adults groups. However, the study by (Rizio & Diaz, 2016) did find differences between 34 younger (mean age 24.11, ± 4.08 years) and 25 older healthy adults (mean age 66.97, ± 4.75 years) when it came to associating the FAT with working memory changes with age.

2.5 Inferior Fronto-Occipital Fasciculus

2.5.1 Anatomy

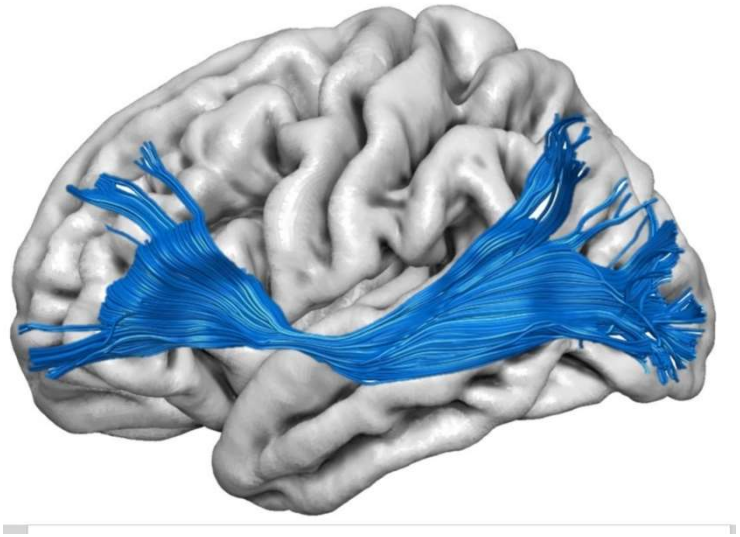


Figure 14 Inferior Fronto-Occipital Fasciculus (IFOF)

Table 1 Cortical termination points of the IFOF in humans, (Thiebaut de Schotten, 2012)

Frontal Lobe	Parietal lobe	Temporal lobe	Occipital Lobe
Medial fronto-orbital region (BA10, & 11); some sections of the rostral superior frontal gyrus BA9); some branching into fronto-lateral regions – particularly anterior inferior frontal gyrus.	Some literature mentions some minor branching in the medial (Catani, Howard, Pajevic, & Jones, 2002) or posterior/superior parietal lobe (Martino, Brogna, Robles, Vergani, & Duffau, 2010).	Regions of the occipito-temporal boundaries – e.g. fusiform and lingual gyri (BA37).	Regions of the occipito-temporal boundaries, fusiform and lingual gyri (BA37). Also posterior occipital cortex (BA18 & 19) including cuneus.

The inferior fronto-occipital fasciculus (IFOF) is an association pathway that connects primarily the frontal and occipital lobes. Both frontal and occipital termination points are fanned out, but towards the mid-section of the tract it narrows as it passes through the external/extreme capsule, running dorsal to the fibres of the uncinate fasciculus (Kier, Staib, Davis, & Bronen, 2004)

There is some variation in the literature as to the exact termination points of the IFOF. Largely all are agreed that the IFOF terminates in polar and orbital regions of the frontal lobe, with some branching to the inferior frontal gyrus and DLPFC (Sarubbo, De Benedictis, Maldonado, Basso,

& Duffau, 2013; Vassal, Pommier, Sontheimer, & Lemaire, 2018). Descriptions of the termination points in the occipital lobe can be quite vague although it seems to be generally agreed that BA18 and 19 are the main cortical regions, as well as the temporo-occipital border of the brain (e.g. posterior lingual and fusiform gyri, BA37) (Catani & Thiebaut de Schotten, 2008, 2012; Forkel et al., 2014; Martino et al., 2010, 2011). Until recently, observations of terminations of the posterior IFOF in the medial or posterior parietal/superior cortex, and branching to the middle and inferior temporal gyri (Catani et al., 2002) have been less unanimous. However, in their systematic investigation into cortical terminations of the IFOF (Vassal et al., 2018) provided one explanation for this. They suggested that there are inter individual differences and lateralization effects that may explain the more sporadic reporting of these anatomical characteristics of the IFOF. In 20 young adults, a varied distribution of cortical terminations was observed:

- Frontal lobe: orbitofrontal cortex and frontal pole (100%), inferior frontal gyrus (65%), prefrontal cortex (65%)
- Occipital lobe: lateral occipital gyri (100%), lingual (90%) and cuneus (90%)
- Temporal lobe: fusiform (90%), inferior temporal (85%) and medial temporal gyri (90%)
- Parietal lobe: superior parietal lobule (80%)

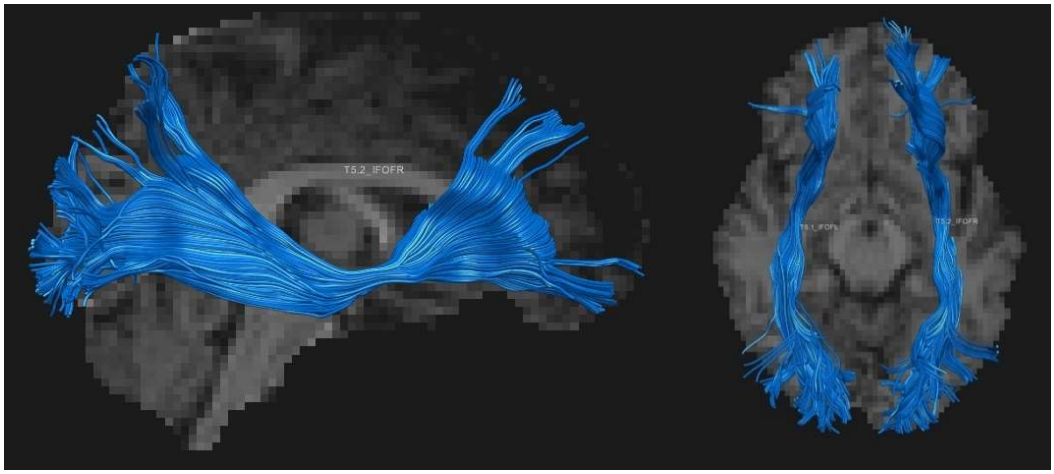


Figure 15 Reconstruction of the lateral and dorsal aspects of the IFOF

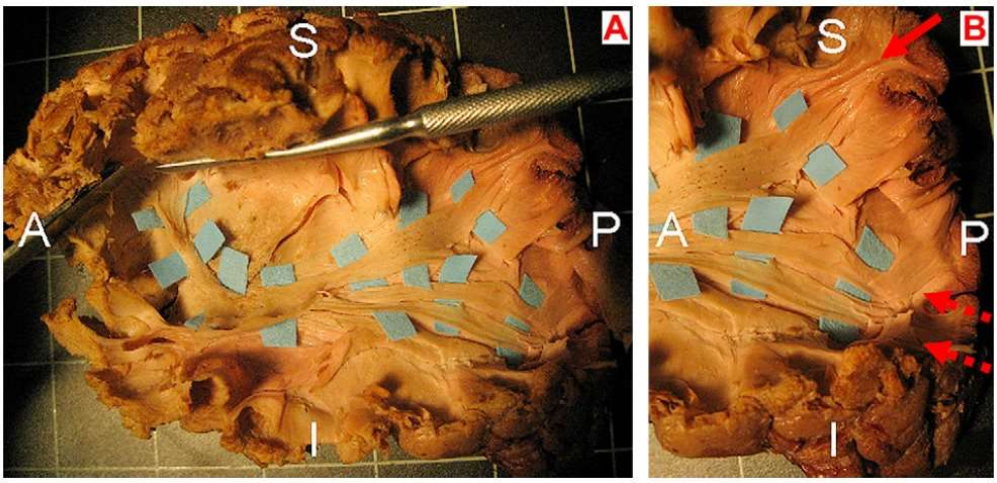


Figure 16 Separation of superficial-dorsal and deep-ventral segments of the IFOF (Martino, 2009)

Through post mortem dissection of 14 hemispheres (seven left and seven right), (Martino et al., 2010) demonstrated that the IFOF can be divided into two 'sub components': a superficial-dorsal (lateral) stream, and a deeper (more medial) ventral stream. They described the superficial dorsal component terminating in the superior parietal lobe (in nine of 14 hemispheres dissected) and the superior and middle occipital gyri. The medial ventral component was described as terminating in the occipital and 'basal' temporal lobe (eight of the 14 hemispheres);

In a later study, five post-mortem brains were dissected (both hemispheres), and a single DTI scan conducted on one healthy adult subject (43 years of age). This work expanded on the described divisions, giving more detail of frontal terminations and suggest further segmentation according to function (Sarubbo et al., 2013). They described a superficial segment connecting the superior parietal and extra-striate cortex of the occipital lobe with the pars triangularis and pars orbitalis (red, Fig. 17). A deeper segment was divided into three further components: A posterior sub-segment connecting the superior parietal lobe, occipital extra striate and fusiform cortices to the middle frontal gyrus and DLPFC (green, Fig. 17); a middle sub-segment connecting the superior parietal lobe and the lateral orbitofrontal cortex and medial frontal gyrus (yellow, Fig. 17); An anterior sub-segment connecting the occipital extra striate cortex and fusiform gyrus with the basal orbito frontal cortex (blue, Fig. 17);

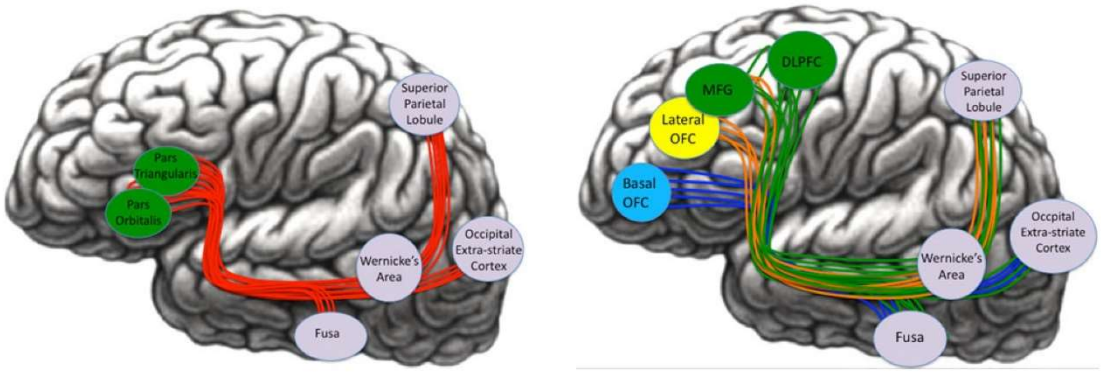


Figure 17 Segmentation of the IFOF according to (Sarubbo, 2013)

The group proceeded to posit that these segments have functionally distinct roles; They assign the superficial segment, and the posterior deep segment to semantic processing; the middle deep segment to integration of sensory and motor information and the anterior deep segment to emotional and behavioural processing;

In more recent study (Panesar et al., 2017) supported the observation that the termination points of the IFOF differed across individuals. They segmented the IFOF into three regions, a superficial 'ventrolateral' segment connecting parietal and occipital lobes to the inferior frontal gyrus, a deep 'dorsomedial' segment splitting out in the frontal lobe to middle frontal gyri and a 'ventromedial' segment reaching more anteriorly towards the orbital (BA11) region of the frontal lobe.

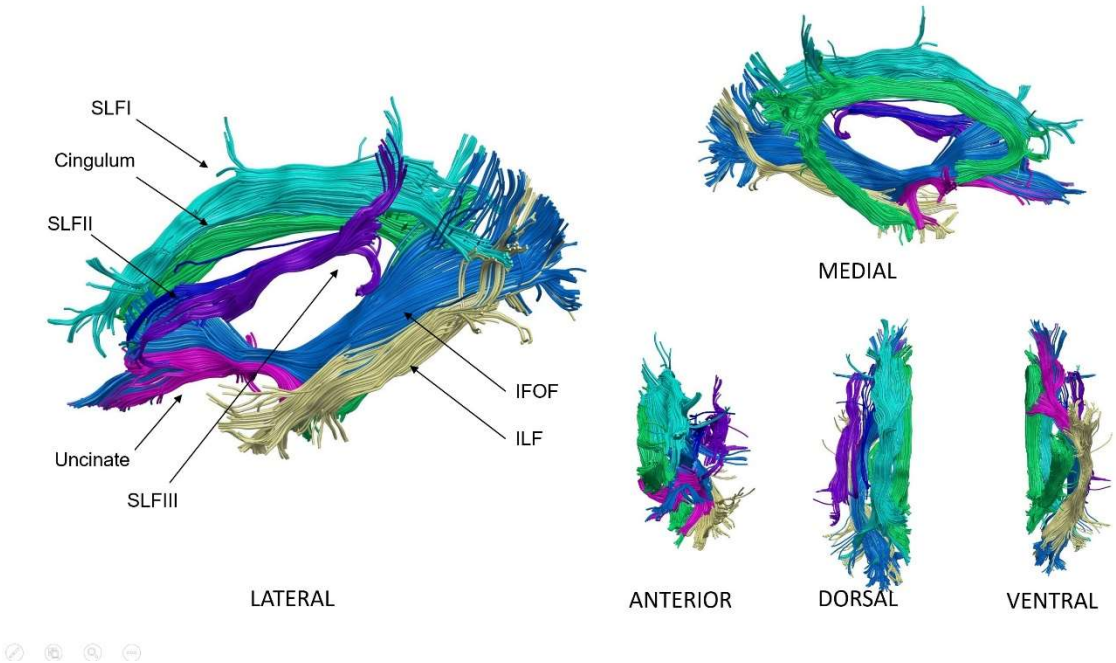


Figure 18 Neighbouring tracts of the IFOF

In the temporal lobe, the IFOF is sandwiched between the para-hippocampal section of the cingulum medially and the inferior longitudinal fasciculus (ILF) laterally. Moving more anteriorly, towards the narrowest regions of the IFOF, it travels through the temporal stem above or dorsal to the uncinate as part of the external/extreme capsule. Frontal fibres of the IFOF may cross with frontal fibres of the SLFI, II and III although there are challenges in fully visualizing these most anterior connections, mentioned by (Martino et al., 2010).

A rightward lateralisation in number of streamlines, but no significant lateralisation in volume or FA (Thiebaut de Schotten, Ffytche, et al., 2011) was been observed in the IFOF of young healthy adults. A later study in a group of 20 healthy young adults between the age of 19 and 40 years, did not find significant differences between left and right IFOF volume, FA, nor tract length. However, what they did find was that the IFOF tended to terminate in the superior parietal lobe in the right hemisphere, but in the inferior frontal gyrus in the left hemisphere (Vassal et al., 2018).

2.5.2 Function

2.5.2.1 Visuospatial processing

In a small case-based study, Urbanski examined two stroke patients (59 and 80 years of age) and explored the relationship between left unilateral neglect and the white matter pathways SLF,

ILF and IFOF. Using DTI tractography they demonstrated that these two appeared to have a complete absence of the right IFOF (Urbanski et al., 2008). In a much larger study of 248 predominantly older adults with sub-acute stroke (26 – 93, with a mean age of 72 years), a different facet of visual attention was measured using the 'Figure copy task'. They found that patients that were impaired in copying the finer detail of the image (see Fig. 19) correlated to damage in the left IFOF (Humphreys & Chechlacz, 2015).

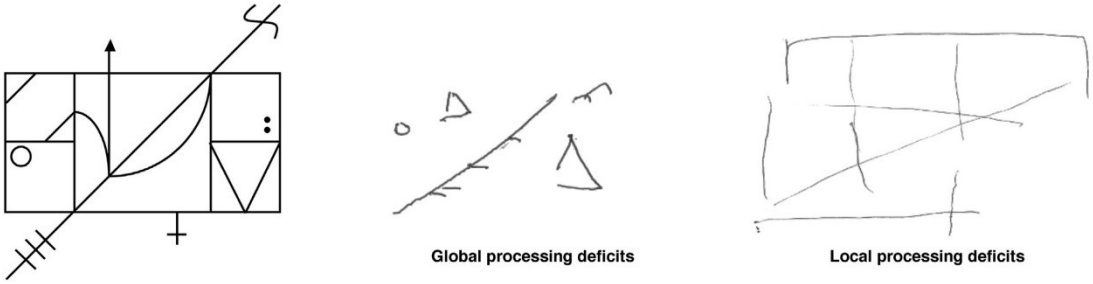


Figure 19 Figure copy task and global and local reproduction deficits (Chechlacz 2015)

2.5.2.2 Working memory

Using voxel based morphometry (VBM) to define and assess integrity of white matter tracts, it was found that reduced spatial span indicated by performance on the Corsi Block Tapping task correlated with disconnection across a group of association pathways, including the IFOF (Chechlacz et al., 2014). This was demonstrated in a group of 57 adult patients (20 -85, mean age 60.5 years) suffering vascular stroke or unspecified vasculitis.

2.5.2.3 Semantic memory, processing and language

A study on healthy older adults (aged 55 – 85 years of age) identified the left uncinate and IFOF as being instrumental in amodal semantic memory (de Zubicaray, Rose, & McMahon, 2011), i.e. the ability to assign a particular meaning to a specific word, object, fact or person. Using data from intra-operative electro cortical stimulation and tractography data, on young to middle aged (17 – 52 years) patients suffering low grade gliomas, one group has suggested that the IFOF plays a role in semantic processing (Duffau, 2008; Duffau et al., 2005; Duffau, Moritz-Gasser, & Mandonnet, 2014).

Other studies support a role for the IFOF in language. For example, one group found that lower MD in the IFOF correlated with learning a second language later in life (Hamalainen, Sairanen, Leminen, & Lehtonen, 2017) on 30 young adults (mean age range 26 – 29 years).

2.5.2.4 Emotion processing

103 patients from IOWA suffering lesions (mean age of approximately 51 – 56 years of age) and 18 healthy age matched controls completed an emotion recognition task (Adolphs, Damasio, & Tranel, 2002). Disconnection of the right IFOF significantly predicted decreased ability to perform this task correctly (Philippi, Mehta, Grabowski, Adolphs, & Rudrauf, 2009). A subsequent study (Yordanova, Duffau, & Herbet, 2017) examined the ability of 27 patients (aged 24 – 65 years) with low grade glioma's to complete the task 'reading the mind in the eyes' which measures face based mentalizing*. Using 'disconnectome analysis (Thiebaut de Schotten et al., 2015) they identified a high probability of reduced connectivity in the IFOF and possibly the SLF/AF as being associated with degraded task performance. *Faced based mentalizing is the ability 'to infer complex mental states from human faces' (Yordanova et al., 2017).

2.5.3 Changes with age

Using a group of 403 healthy participants (aged 5 – 83 years) (Lebel et al., 2012) found that the IFOF was one of the earliest association tracts to reach peak FA and Volume and lowest MD (in the mid to late 20's). FA declined and MD increased steadily after the age of around 30 years. IFOF volume started to decline much later – between 50 – 60 years of age (see Fig 20)

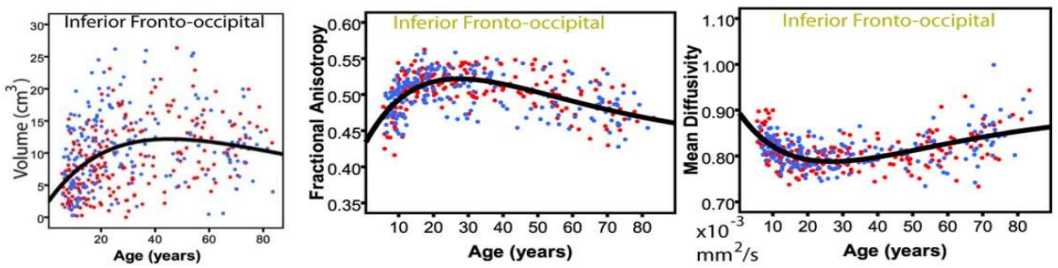


Figure 20 Changes in IFOF volume, FA and MD with age (Lebel 2012)

Several of the studies already mentioned previously describe impaired connectivity of the IFOF in older adults who have suffered stroke. In a different patient group, 64 subjects suffering from three forms of Alzheimer's disease ('Dementia of the Alzheimer's Type, Primary Progressive Aphasia and Posterior Cortical Atrophy), a network of white matter pathways were found to

increase in MD, including the IFOF (Madhavan et al., 2016). Less is found in the literature concerning healthy aging and the IFOF. However, one study looked at set shifting performance changes with age measured by the Trail Making Test (B). A group of 24 healthy adults (21 – 80 years of age) demonstrated reduced performance with age, and this found to be mediated by a decline in FA for the corpus callosum, corticospinal tract, SLF, uncinate and IFOF.

In a study measuring cognitive performance of 296 healthy subjects (aged 8 – 68 years, mean age 29.6), changes in FA of the cingulum and IFOF were associated with executive function and global cognitive functioning, independent of age. After adjustment for speed of processing however, the IFOF no longer played a significant mediating role in the age-cognition relationship (Peters et al., 2014).

2.6 Superior Longitudinal Fasciculus

2.6.1 Anatomy

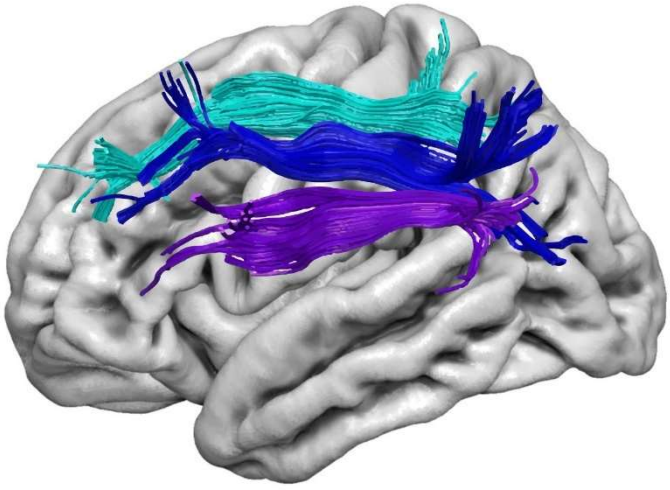


Figure 21 Superior Longitudinal Fasciculus (SLF) system

A set of fronto-parietal white matter connections in the monkey brain has been established firmly for many decades. However, the superior longitudinal fasciculus (SLF) in the human brain has only recently been described in vivo using Spherical Deconvolution (SD) techniques. Furthermore, there is a certain amount of confusion in the literature surrounding the exact anatomy of the SLF in humans due to the close positioning of the segments alongside several other white matter pathways such as the cingulum and the arcuate. This chapter aims to provide some context and clarification as to the anatomy of the SLF, as well as providing an overview of the potential functions of this pathway.

To understand some of the conflicting views in current literature regarding the anatomy of the SLF it may help to be aware of some historic context. In the early 1800's Reil, and Burdach both began to describe white matter fibres connecting the frontal, parietal and temporal regions (Catani & Mesulam, 2008). What they were describing was what is now accepted to be the Arcuate Fasciculus, or 'language pathway'. Towards the end of the same century, Dejerine (Dejerine & Dejeine-Klumpke, 1895) provided a detailed description of the same white matter pathway in chapter 5 of his first volume of 'Anatomie des Centres Nerveux'. However, Dejerine also used another term to describe this pathway: the superior longitudinal fasciculus. This interchange of the terms 'arcuate' and 'superior longitudinal' still continues today within some schools of thought,

whilst others have started to separate out the two terms and assign anatomically separate trajectories to each one.

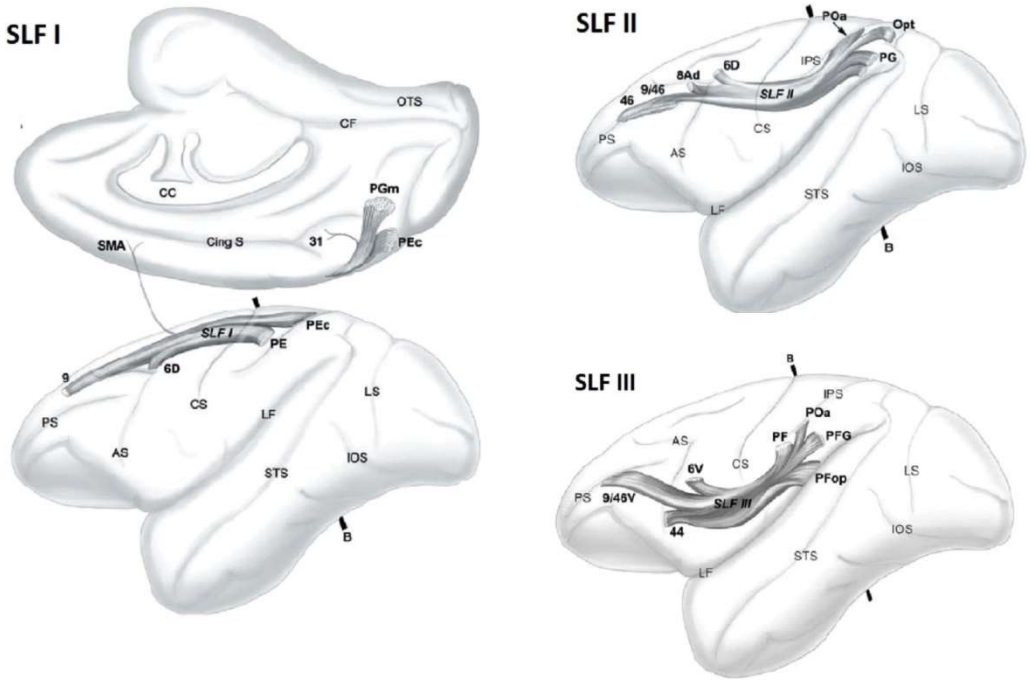


Figure 22 Segmentation of the SLF system in the macaque (Schmammann 2007)

Table 2 Anatomical landmarks of the SLF system in the macaque (Schmamman, 2007)

Tract	Frontal Lobe	Parietal Lobe
SLFI	• Dorsal section of premotor (6D), supplementary motor area (SMA) and prefrontal cortices; (9) and the medial premotor region (31)	• Medial (PGm) & superior parietal lobules (PE & PEc)
SLFII	• Caudal prefrontal cortex (dorsolateral areas 6D, 8Ad and 9/46 and 46)	• Caudal part of the inferior parietal lobule PG/Opt and occipito-parietal area POa)
SLFIII	• Ventral premotor area 6V & 44 ventral prefrontal area 9/46	• Rostral part of the inferior parietal lobule (PF, POa, PFG and PFop)

(Petrides & Pandya, 1984) used axonal tracing methods to examine the pathways originating in the posterior parietal cortex of 19 rhesus monkeys. Petrides refers to ‘three relatively distinct fibre systems’ connecting parietal and frontal regions. Later (Schmahmann et al., 2007) used autoradiography and compared these results with diffusion spectrum imaging (DSI) methods and described again 3 distinct fronto-parietal pathways in monkey brains (see Fig. 22 and table 2).

Incidentally, they argue that SLF pathways are separate and distinct from the arcuate, which they describe as connecting frontal and temporal regions.

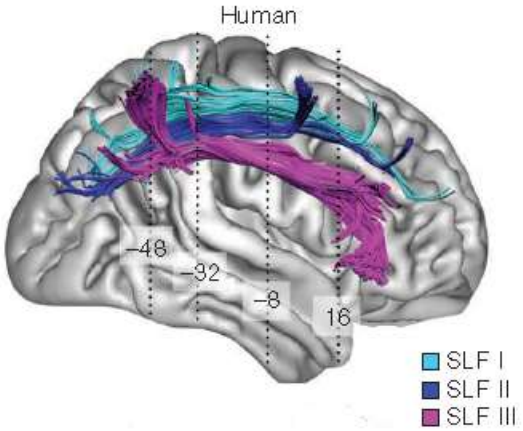


Figure 23: Segmentation of the SLF system in the human (Thiebaut de Schotten 2011)

Table 3 Anatomical landmarks of the SLF system in the human (Thiebaut de Schotten 2011)

Tract	Frontal Lobe (Brodmann's area)	Parietal Lobe (Brodmann's area)
SLFI	• Anterior cingulate (BA32, and possibly BA42? • Superior frontal gyrus (BA8 & 9)	• Precuneus (BA5 & 7); • Superior parietal lobe (BA5 & 7)
SLFII	• Posterior regions of the superior and middle frontal gyri BA6, 8 & 9)	• Anterior intraparietal sulcus (BA40) • Angular gyrus BA39 (inferior parietal lobule)
SLFIII	• Inferior frontal gyrus (BA 44, 45, 47)	• Anterior intraparietal sulcus (BA40) • Inferior parietal lobule

In humans however, separating out fronto-parietal pathways from the well-known arcuate has only recently begun to be suggested. For example in 2002 (Catani et al., 2002) produced white matter atlas papers describing initially 10 pathways, including the arcuate, which they also termed as the superior longitudinal fasciculus. In 2008 (Catani & Thiebaut de Schotten, 2008) provided guidelines to delineate the ROIs, but this time referred to the Arcuate and did not mention the SLF. However in 2012, with the advent to Spherical Deconvolution (SD) methods a white matter atlas was authored by (Catani & Thiebaut de Schotten, 2012) which separates out the arcuate and the SLF into different systems. The authors justify their departure from Dejerine's and their own original collation of the SLF and Arcuate into one pathway by referring to the new capabilities

of SD and comparing this data to axonal tracing studies in monkeys (Pandya & Kuypers, 1969) alongside other electrophysiological recordings studies. However, in 2012, they still suggested some overlap between the SLF and Arcuate by indicating that the SLFIII is the same pathway as the anterior segment of the arcuate fasciculus.

In Thiebaut de Schotten's communication paper (Thiebaut de Schotten, Dell'Acqua, et al., 2011) he uses Spherical Deconvolution methods (Dell'Acqua et al., 2010) to produce tractography data with sufficient detail to be able to delineate and describe the course of all three SLF pathways in the human (compared to the SLF system described in monkey species) in greater detail. This dissection protocol outlined in the supplementary material is the one that has been adapted for this analysis.

There are other perspectives and anatomical interpretations however in the literature. Makris et al, (Makris et al., 1997) base their anatomical definition of the SLF on Dejerine's original descriptions. However, in a subsequent paper (Makris et al., 2005) this description is adapted and expanded. The SLF is defined as 4 segments or 'white matter blades'; 3 connect fronto-parietal lobes and the 4th represents the arcuate and is located in the parietal / temporal junction. (Oishi et al., 2008) based their understanding of the SLF on Markri's '4 blade' interpretation. They extend their description of the SLF by using an atlas to compare healthy controls with AD patients. The John Hopkins University School of Medicine and collaborators have produced several white matter atlas publications within the last two decades. (Mori et al., 2002) published their debut description of association pathways using DTI in 2002. The superior longitudinal fasciculus in Mori's paper follows the path of the arcuate fasciculus. (Wakana et al., 2004) follow's Mori's description of the to the superior longitudinal fasciculus, the anatomy described matching that of the arcuate fasciculus. In subsequent years, (Mori et al., 2008) produced an updated atlas, again assigning the SLF to the same trajectory as the arcuate.

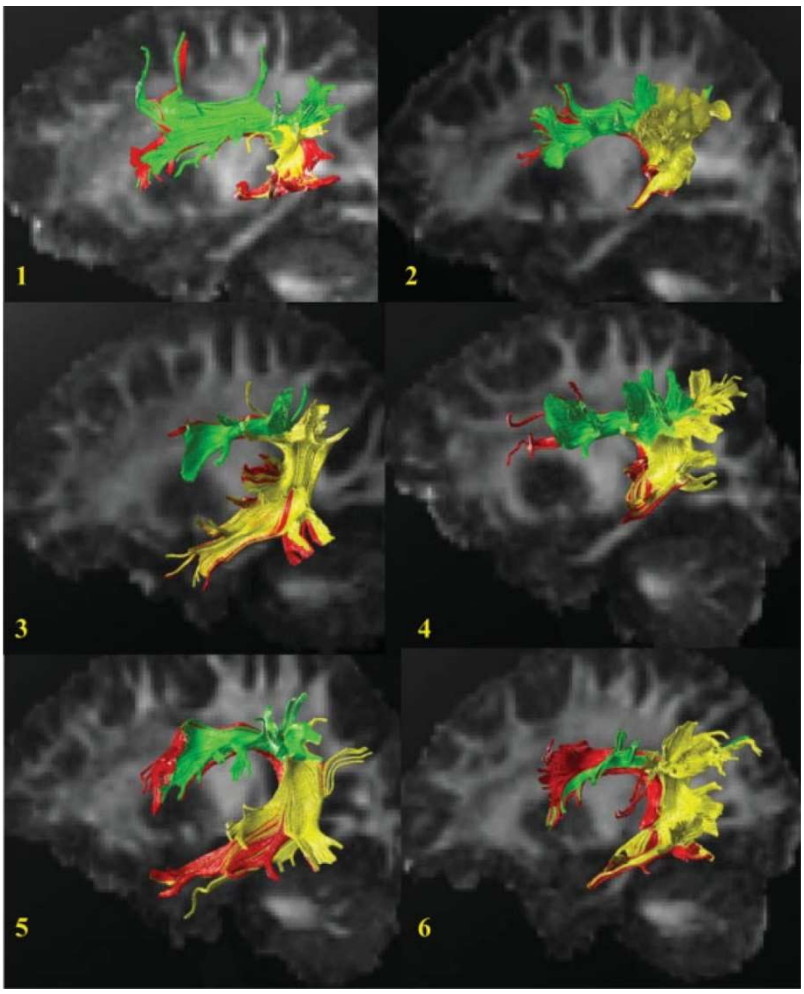


Figure 24 Three segments of the arcuate in 6 individuals, (Catani 2005)

The arcuate fasciculus, while often still defined as a single pathway connecting fronto, parietal and temporal cortices together, has by some researchers been divided into three segments. Figure 24 provides an illustration of these segments how they vary across individuals but also how the anatomy is similar to the more ventral segments of the SLF system. The anterior segment of the arcuate (green, Fig 24) described by (Catani et al., 2005) originates in the inferior frontal gyrus (BA44 & 45) as well as areas of the inferior precentral gyrus and posterior middle frontal gyrus and connects to the inferior parietal lobe (BA 39, supramarginal gyrus and BA40, the angular gyrus). The approximate termination points fall within the same broad cortical regions as the SLF III. However, it has not quantifiably been demonstrated that exact trajectories of both these pathways vary or are the same. Nor has a definitive comparison of positioning of the termination points between these two pathways been conducted. One of the reasons for this delay is that while SD methods provide greater visibility of the SLF system, they result in a larger number of false positive artefacts in the arcuate. Further work needs to be done to reconcile this disparity in dissection methods, but this is not within the scope of this study.

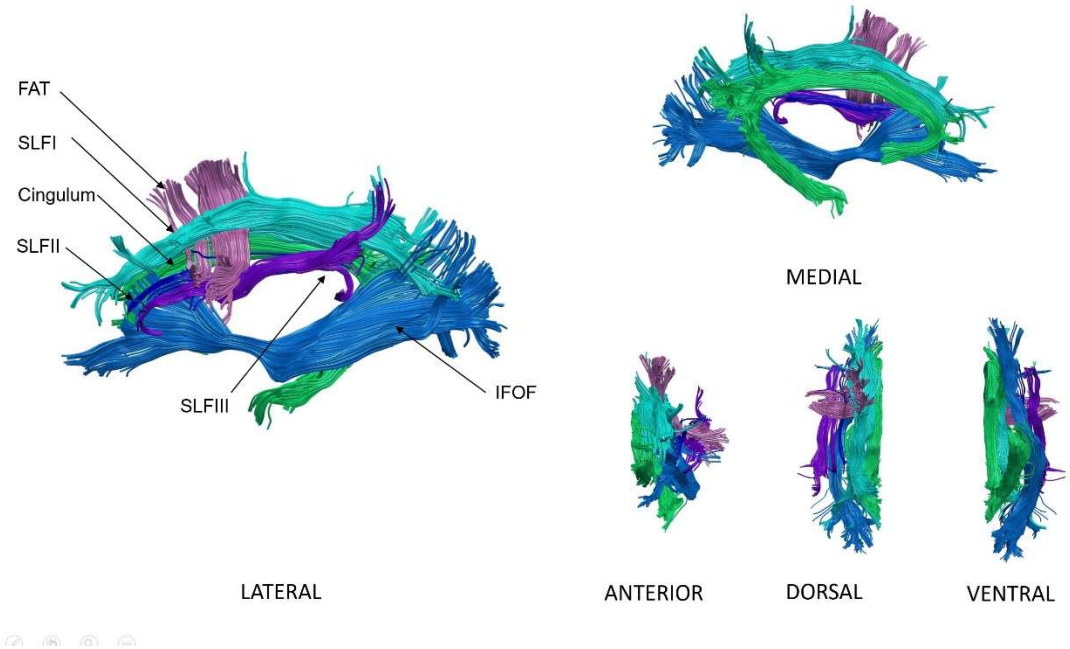


Figure 25 Neighbouring tracts of the SLFI and II

In addition to the close proximity or overlap of the SLFIII and the anterior segment of the arcuate other neighbouring tracts are the cingulum, which lies medial and slightly ventral to the SLFI. Differentiation between these two tracts can be challenging. In the frontal lobe, the FAT traverses' ventral to all three SLF segments. There is some potential overlap also between the frontal termination points of the IFOF and the SLF system.

2.6.2 Function

In the literature functions of the SLF system are sometimes attributed to individual segments (e.g. SLFI or SLFII) and sometimes to pairs of segments. Outlined below is an overview of these findings.

2.6.2.1 Motor function

The SLFI connects the medial SMA, and posterior regions of the superior frontal gyrus with the precuneus and superior parietal lobule. These frontal regions are responsible motor initiation and regulation. The superior parietal regions are responsible for somatosensory processing and spatial orientation. The SLFII connects the posterior regions of the superior and middle frontal gyrus with the intraparietal sulcus and inferior parietal lobe (angular gyrus). These frontal regions include the human frontal eye field (FEF), pre-motor cortices and part of the prefrontal cortex. The

SLFIII connects the posterior Inferior frontal gyrus with inferior parietal lobe. (Budisavljevic, Dell'Acqua, Zanatto, et al., 2017) found an association between SLFII and SLFIII volumes and visuomotor processing in 30 healthy young adults (aged 24.6, ±2.8 years). In a meta-analysis (Parlatini et al., 2017) found a correlation between the SLFI and SLFII and spatial and motor function. (Howells et al., 2018) recently explored the relationship between the lateralisation of the SLF system with lateralized hand preference in tasks requiring visuospatial processing and fine motor control.

2.6.2.2 Visuospatial attention

The inferior parietal lobe is responsible for spatial attention. It has been well documented that patients with lesions in this area can suffer from neglect (Behrmann & Shomstein, 2015; Beis et al., 2004; Karnath & Rorden, 2012; Mesulam, 1999; Ten Brink et al., 2016). A large body of literature suggests that the neurobiological correlates of visuospatial attention are predominantly rightward lateralised in humans. In their review (Corbetta & Shulman, 2002) posit that there are two fronto-parietal networks involved in this function. A dorsal, 'top down' cognitively driven fronto-parietal network controlling visuo-spatial attention and a ventral, (right lateralized), 'bottom-up' network that operates as a 'circuit breaker' of the dorsal network.

(Thiebaut de Schotten, Dell'Acqua, et al., 2011) started to explore further a specific role for the SLF system in visuospatial attention, using the line bisection task and an adaptation of the Posner paradigm. With 20 young adult participants, he found that an increased size of the right SLFII correlated directly with a greater leftward deviation in the line bisection task for 17 of the participants; Conversely, three participants that deviated more to the right correlated with a larger left SLFII volume. He suggests that larger tract volume could be associated with better myelination or more axons, or larger axon diameter. This could lead to faster conduction speed. To test the hypothesis that faster processing speed of the SLFII resulted in a bias towards the left or right (as appropriate) further analysis was conducted. He looked at performance of the Posner paradigm in response to cues in the left side of the screen and found that quicker detection times were related to a larger SLFII in the right hemisphere; and that greater deviation to the left in line bisection (associated with a larger SLFII Right in previous analysis) related to faster detection times to cues on the left side of the screen. (Thiebaut de Schotten, Dell'Acqua, et al., 2011) further suggested that the overlap of the SLFII between SLFI and SLFIII provides a communication

between dorsal and ventral ‘networks’ discussed by (Corbetta & Shulman, 2002) in their goal directed and stimulus driven theory of visual spatial attention.

2.6.2.3 Language

In a review (Alan Baddeley, 2003) ascribes frontal (BA6/44) and tempo-parietal (The inferior parietal lobe BA40) regions to be involved in the ‘phonological loop’ aspect of his executive function model. These regions are connected by the SLFIII. In their meta-analysis (Parlatini et al., 2017) found associations between the SLFII and SLFIII and language associated tasks such as semantic and phonological processing as well as verbal working memory.

2.6.2.4 Working memory

Previous studies have identified the DLPFC, i.e. BA46 as the area for working memory in general (e.g. .verbal and visual). (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998) conducted an fMRI study on 11 subjects to explore the neurobiological correlate of *spatial* working memory in humans in particular. They found that the superior frontal *sulcus*, anterior to the frontal eye field was activated specifically during spatial WM task, as opposed to other visual working memory tasks (e.g. facial working memory). As previously mentioned (Parlatini et al., 2017) found associations between the SLFII and SLFIII verbal working memory function.

2.6.3 Changes with age

At the time of writing, studies addressing the aging trajectory of the human SLF system as described by (Thiebaut de Schotten, Dell’Acqua, et al., 2011) were not found in the literature.

2.7 Uncinate

2.7.1 Anatomy

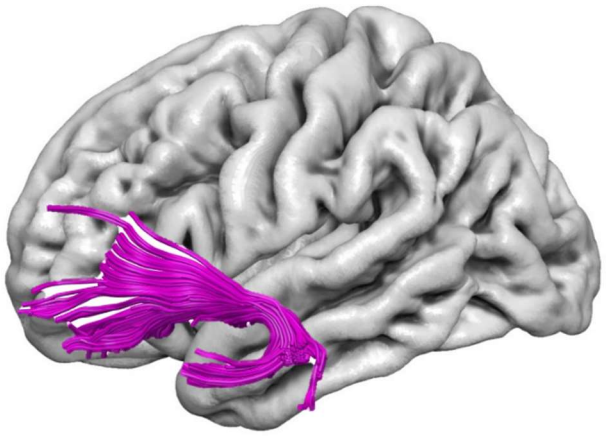


Figure 26 The uncinate

Table 4 Cortical termination points of the uncinate in humans

Frontal Lobe	Temporal lobe
Orbital and Polar frontal cortex (BA10, 11, 47)	Anterior temporal lobe (BA 20 & 38) Uncus (BA35) para-hippocampal gyrus, (BA30, 36)

The uncinate is a small association tract connecting two regions of the anterior frontal cortex with the anterior temporal lobe. A ventro-lateral branch is located in the lateral orbitofrontal cortex and a more medial branch is located in the frontal pole leaning towards the anterior cingulate gyrus. As these two branches travel posteriorly, they gradually merge, passing through the external/extreme capsule, inferior to the IFOF. Just beyond this point, they make a 'u-bend', switching course and travelling slightly ventrally and laterally into the anterior temporal lobe (Catani & Thiebaut de Schotten, 2012). Termination points in the temporal lobe range from the temporal pole, to the more medial uncus, para-hippocampal gyrus and cortical nuclei of the amygdala (Ebeling & von Cramon, 1992; Klinger & Gloor, 1960).

(Ebeling & von Cramon, 1992) divides the uncinate into ventral (grey) and dorsal (white) sections (Fig. 27). However, it is not clear why this segmentation has been described and if there is any functional relevance.

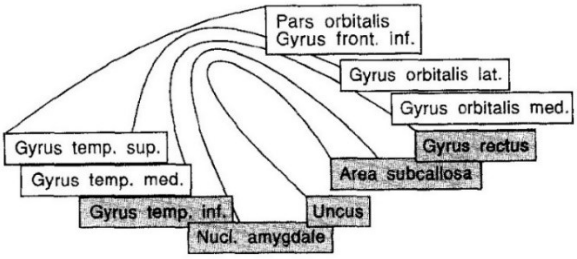


Figure 27 Ventral (grey) and dorsal (white) sections of the uncinate (Ebeling, 1992)

Recent work by (Hau et al., 2017) suggests a more finely detailed perspective on the uncinate anatomy and propose it's segmentation into five different sections.

At the medial frontal termination points, the uncinate is proximate to the anterior termination points of the cingulum but it is not certain that fibres from these two tracts connect directly (therefore not included in Fig. 28). As the uncinate travels posteriorly into the external/extreme capsule, it lies inferior to the IFOF (blue). The central 'hook' region of the uncinate is close to the left fibres of the anterior commissure (not included in Fig 28). Its temporal termination points are medial to the temporal termination points of the ILF (yellow).

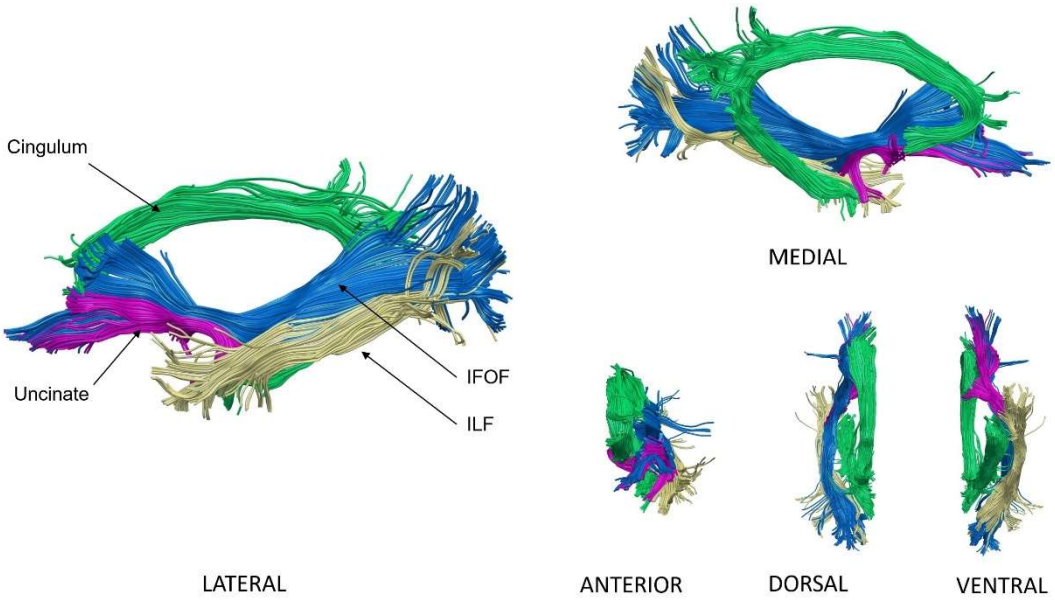


Figure 28 Neighbouring tracts of the uncinate

A rightward lateralization (right larger than left) of uncinate volume was reported (Highley, Walker, Esiri, Crow, & Harrison, 2002) in a study on 21 post mortem brains of older adults (mean age 74.5 SD12 females; 70.0 SD 14.1 males). However, in a slightly larger study of 40 young adults (between 18- 22 years old) no significant asymmetries were identified using DTI for volume or FA (Thiebaut de Schotten, Ffytche, et al., 2011).

There are equally equivocal findings for uncinate microstructure. Leftward FA lateralization (higher FA in left compared to right uncinate) was reported in 10 healthy controls (approximately young to middle aged adults) by (Diehl et al., 2008). This is supported by other studies (Hasan et al., 2009; Kubicki et al., 2002). However, a rightward FA lateralization (higher FA in right compared to left uncinate) has been observed in 32 healthy subjects (aged between 28 – 53, mean 44 years) (Park et al., 2004) and in another smaller study 10 healthy adults (20 – 30 years, mean 23 years) (Rodrigo et al., 2007).

2.7.2 Function

The uncinate is primarily associated with memory, language and social and emotional processing. However, there are other more recent findings that suggest it could be involved in a broader range of functions.

2.7.2.1 Language

In a review of a series of studies using electrostimulation during surgery, a theory that there are separate dorsal and ventral streams involved in language was described (Duffau, 2008). The group suggest that the SLF/arcuate is involved in a 'dorsal stream' and that the IFOF is involved in a ventral stream of language processing. In a subsequent study using data collected from a group of 13 patients (aged 26 – 60, mean 38 years) during intraoperative electrostimulation (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009), semantic paraphasia* was generated in half the group when stimulating the IFOF and the other half when stimulating the uncinate. This same group of authors later suggested that the uncinate is part of an indirect, inessential semantic ventral stream' (Duffau et al., 2014).

* (Stemmer & Whitaker, 2008) describe paraphasia as when an alternative, but a semantically appropriate word is spoken in place of the intended one - i.e. uttering 'magazine' instead of 'book'.

A similar relationship was observed in a case report (Nomura et al., 2013) where object naming, alongside verbal paraphasia and perseveration occurred during electrical stimulation of a region close to the left uncinate during surgery on a 39 year old male patient requiring resection of an astrocytoma. In addition, naming of famous faces and objects was impaired in in a subset of 44 patients with low grade glioma (24 – 70 years, mean 41.18), where 18 had their uncinate fasciculus removed as part of their surgery. This functional deficit remained in 17 of the 18 participants (who had not suffered a recurrence of the glioma) in a follow up study (Papagno et al., 2016).

2.7.2.2 Emotion processing

The uncinate has been associated with a range of emotional processing functions or dysfunction in relation to emotional regulation or expression. For example in a healthy population of 194 young adults (mean age 19.66 ±1.3 years) use of the process 'reappraisal' (reappraisal is a strategy whereby the context of an emotional experience is 'reframed' in some way) was positively correlated with FA values in the bilateral uncinate (Zuurbier, Nikolova, Ahs, & Hariri, 2013). On the opposite side of the coin, the uncinate is associated with pathology in regards to social and emotional processing, for example in conduct disorder (Sarkar et al., 2013) in adolescents and psychopathy in adults (Craig et al., 2009).

In 29 patients with either deficit (primarily negative symptoms*) or non-deficit (mean age 32.36 ± 8.23 and 40.70 ± 12.27 mean years respectively) Schizophrenia and 17 healthy controls (33.82, ± 10.11 mean years), FA of the uncinate was investigated using DTI. The study found that the patient group with deficit Schizophrenia (11 subjects) had lower FA in the left uncinate (Kitis et al., 2012) compared to the non-deficit group and controls. [* negative symptoms include 'restricted affect, reduced emotional range, poverty of speech, curbing of interest, reduced sense of purpose and reduced social drive].

(Hornberger, Geng, & Hodges, 2011) compared a group of 14 behavioural variant fronto-temporal dementia (FTD) patients (mean age 59.3 SD 7.9 years), exhibiting disinhibition, and a group of 15 AD patients (mean age 63.8 SD 7.7 years). FA values for the anterior corpus callosum and uncinate negatively correlated with number of errors on the Hayling test (measuring disinhibition) for the FTD group.

2.7.2.3 Working memory

FA of the left uncinate was found to be associated with performance of the digit span and verbal fluency tasks in a group of 14 Patients (mean age 34 years ± 8.15) with temporal lobe epilepsy and age matched healthy controls (Diao et al., 2015). Using voxel-based statistical (VBS) analysis, a group investigating working memory in 99 middle aged to older adults (50 – 89 years) (Charlton et al., 2010) found that MD of frontal, temporal and parietal cortices were associated with performance in two working memory tests within the Weschsler Memory Scale III (digit span backwards and letter-number sequencing). The uncinate was one of the tracts associated with these regions.

2.7.2.4 Attention

Among several computerised cognitive tests (including spatial memory, sensorimotor dexterity and emotion processing) performance on tasks measuring attention correlated positively with FA of both the left and right uncinate (Singh et al., 2016) in 14 patients (25 – 45, mean 24.14 ± 7.60 years) with Schizophrenia. However, no significant correlations were identified between cognition and changes to microstructure of the uncinate in the age matched healthy controls.

2.7.2.5 Episodic memory

14 Patients with Schizophrenia (mean age 45.5 ± 8.43 years) and 14 age matched controls (mean age 43.9 ± 8.55 years) underwent neuropsychological assessment and DTI scans (Nestor et al., 2004). In the patient group impaired performance in episodic memory tasks correlated with lower FA in the left uncinate. A larger study focusing on 41 healthy subjects (20 – 60 years) also found correlations between memory performance and the left uncinate (Sato, Maruyama, Hoshida, & Minato, 2012).

2.7.3 Changes with age

In a group of 108 healthy subjects including 69 healthy adults (aged 19.9 – 68.3 years), changes in volume, axial diffusivity (AD), radial diffusivity (RD) and FA were measured across the lifespan (from 6 – 68 years of age). Whilst the best fit for changes in FA and Volume across the whole age group was a quadratic curve, when separating out children and adults linear models were more suitable (Hasan et al., 2009).

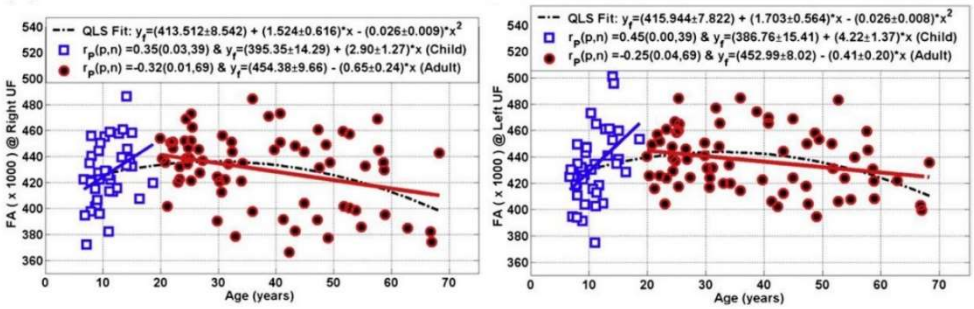


Figure 29 FA of the Left and Right uncinate across the lifespan (Hassan 2009)

In a later study (Fig. 30) involving 403 healthy subjects (aged 5 – 83 years) similar trajectories were observed (Lebel et al., 2012).

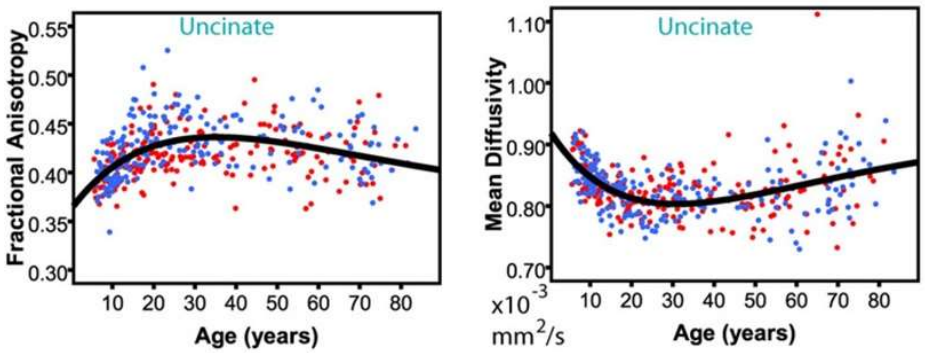


Figure 30 Changes in white matter microstructure of the uncinate (Lebel 2011)

2.8 Summary

To date the white matter pathway with the greatest range of evidence for involvement in executive function including facets such as working memory and attention seems to be the cingulum. However, all of the tracts (including the corpus callosum) in this study have had at least one association with either directly EF or working memory or some form of attention. However, the evidence is still reasonably sparse and there is still much to be learnt.

Chapter 3 Methods

The work reported in this study represents part of a larger 'parent' project called BRCATLAS that gathered a large range of neuroimaging data and behavioural measures. This chapter will give an overview of the ethics, recruitment and general data collection processes for the entire parent study (sections 3.1 and 3.2). It will then provide details about the neuroimaging and behavioural measures specific in this current 'child' study. The current 'child' study is divided into two parts. Chapters 4 and Appendix F focus on the refinement of manual and automated dissection protocols and refer to a small subset of scan only data sets. Chapter 5 uses the larger data set accessing both spherical deconvolution methods and behavioural measures to assess tract-task relationships and how they may alter with age. A complete list of all data collected as part of the wider parent study can be found in Appendix E for interest/reference.

3.1 Ethics

Participants for this study were recruited under the ethics application approved by the King's College London Psychiatry, Nursing and Midwifery Research Ethics Committee in 16th September 2011 (PNM/10/11-146) (Appendix D). An amendment in September 2012 was made to broaden the recruitment methods through advertising in local and national newspapers and through other local gatekeeper organisations and through contacting healthy participants (who had previously consented to being contacted) of other studies conducted at the Institute of Psychiatry, Psychology and Neuroscience (IOPPN). This amendment was approved in 2012.

The study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subject, adopted by the General Assembly of the World Medical Association, 1996.

3.2 Study protocol

3.2.1 Study location

All scans and assessments were conducted either at the Centre for Neuroimaging Sciences, or at Mapother House, (IOPPN), King's College London.

3.2.2 Anonymization procedures

At screening each participant was given a unique identifier code and that code was assigned to all data collected during the study (i.e. for scan acquisition and neuropsychological assessment). An encrypted spreadsheet was used to track participant names and associated unique identifier codes by select research study personnel only. The spreadsheet is stored on the King's College London secure server.

3.2.3 Storage of sensitive data

Participant personal data was kept separate from study data. Participant signed consent forms were also retained for study records. Electronic files containing participant personal information were encrypted. Hard copies were held in a secure location (locked) within the Centre for Neuroimaging Sciences.

3.2.4 Information for participants about the study

A copy of information sheets given to participants can be found in Appendix D

3.2.5 Participants

A total of 104 healthy adults between the age of 18 and 79 years were recruited for this study. Of these, a subset of 18 participants (aged between 19 and 67) were used in the dissection protocol reliability study (Chapter 4). A separate group of 86 participants aged between 18 and 79 were used for the remaining analysis (Chapter 5).

Table 5 Participant age and sex

	Range	**Mean**	**SD**
Age	18 -77	40.65	17.38
Sex (Male, Female)	-	44 (M), 42 (F)	-

3.2.6 Recruitment

Healthy participants were successfully recruited through media advertisements, posters and e-mail invitations to the following groups:

- King's College London students and staff e-mail invitations

- Mindsearch website (subsequently closed)
- SAGA website
- University of the third age, London
- Posters placed in Camberwell, at the IOPPN and King's College Hospital.

Copies of advertisements and posters can be found in the Appendix D

3.2.7 Initial contact and screening questionnaire

Once a volunteer contacted the recruitment team either by phone or by e-mail, they were told briefly about the study and basic eligibility checks were made. They were then sent the information sheet to read. The participants were given the opportunity to ask further questions about the study at any time. After reading the information sheet, if the participant wanted to volunteer, they were asked to complete over the phone a short screening questionnaire (Appendix D) which asked for a brief medial history and checked MRI contraindications. If the participant passed the screening criteria, the researcher explained what would happen during both visits and answered any questions and a time was agreed for the first visit.

3.2.8 Exclusion criteria

Participants were excluded from participating in the study for the following reasons:

- Any history of neurological or psychiatric problems based on self-report (including head injury with a loss of consciousness, as well as participants who considered themselves healthy but were currently taking medication to treat cardiovascular illness, diabetes or hormone depletion).
- Drug/alcohol abuse, number of cigarettes smoked per day.
- Those who had taken for prolonged periods in the recent or not so recent past recreational drugs.
- MMSE score < 26
- Difficulty in completing the training on the cognitive tasks
- Difficulty in complying with the study requirements
- MRI contraindications, including
    - received metal injuries to the eyes,
- had metallic or electronically, magnetically or mechanically activated objects (including clips, pacemakers) inserted to their body at an operation

- have a fear of enclosed spaces,
- have facial tattoos,
- extensive dental work, or
- received shotgun or shrapnel injuries.

Participants over 60 years of age were asked to take the Mini Mental State Exam (MMSE) during their first visit. All participants scored 26 or above.

Participants were either native English speakers or bilingual with good speaking and comprehension of the English language.

Participant IQ was tested using Ravens Standard Progressive Matrices (RPM) (see Appendix E).

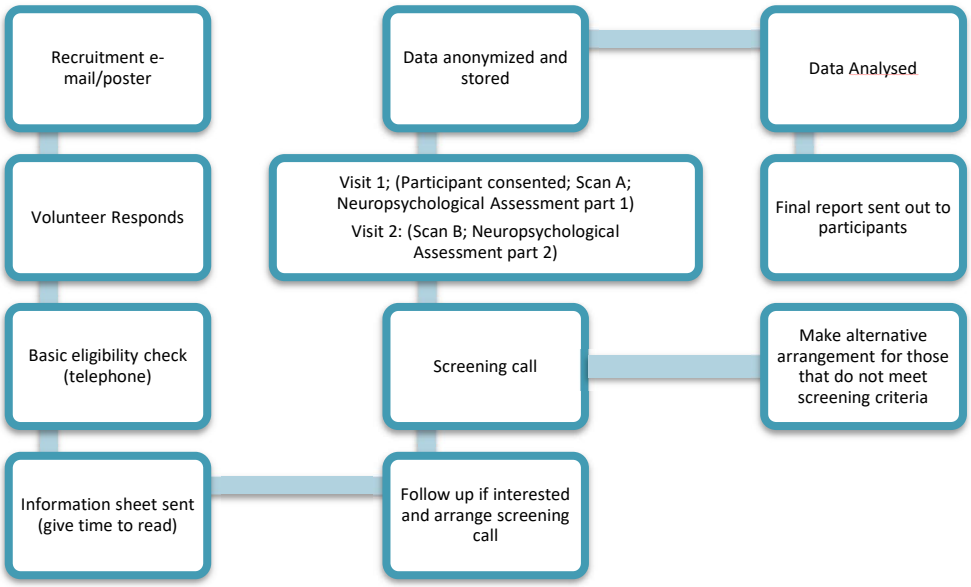


Figure 31 Study protocol

3.2.9 Participant expenses and compensation

Participants received reimbursement for travel expenses for both visits. They were asked to retain and travel or lunch receipts for each visit. In addition, each participant received £20 at the end of the first visit and £36 at the end of the second, longer visit (A total of £56 plus any reasonable travel costs) to recompense their time and involvement in the study.

3.2.10 Participant withdrawal

Participants were informed that they could withdraw from the research project at any time and would not be required to provide a reason. They were able to do this over the phone, in person or in writing. A statement was included in the information sheet to indicate that for participants withdrawing from the study, their data might be used in anonymised form after a certain deadline as it may already have been used in analysis sent for publication. In regard to withdrawal of blood samples, on request, these were destroyed by incineration.

3.2.11 Power calculation

A sample size of 80 participants was calculated at the start of the study. This number allowed linear associations with age to be detected with a Pearson's r=0.31 and above, $\alpha = <0.5$ with power = 0.80.

3.3 Neuropsychological assessment

Neuropsychological assessment took place at the Centre for Neuroimaging Sciences building in an interview room in two visits. (Except for one participant who did part of the neuropsychological assessments in a similar interview room in a nearby building due to lack of availability of the usual facilities)

During the first visit participant were asked to complete the Ravens Progressive Matrices (RPM), Mini Mental State Exam (MMSE), Edinburgh Handedness, Barret Impulsivity and Eysenck Personality questionnaires.

During the second visit, participants completed the remaining tasks. If a participant appeared to be tiring, the participant was offered additional breaks. If deemed appropriate, not all tasks in the second visits were completed. The order of tasks in visit 2 were rotated randomly to avoid bias. However, within the Cambridge Brain Sciences task suite, the order remained stable. This was due to time constraints in setting up the study initially.

3.3.1 IQ: Ravens standard progressive matrices

The Ravens (Standard) Progressive Matrices (RPM) is a nonverbal test to assess a person's eductive general intelligence. It was initially developed by J Raven in 1936, and first published in

1938. It consists of 60 multiple choice questions, increasing in difficulty as the participant works through the book. Each question requires the identification of a missing piece to complete a geometric pattern. The test has been used across numerous cohorts over the last 70 plus years. There are several different versions of the RPM, the Standard (as described above), the Coloured RPM (reduced difficulty) and the Advanced RPM, however it was deemed that the Standard test would be most suitable for the current study cohort of healthy adults.

Test procedure: Instructions were read out to participants as per the Ravens Progressive Matrices (R-SPM) manual. Participants were asked to answer 60 questions using a separate answer sheet. They were informed that they could take as long as they needed. In practice, that task took between 45 – 60 minutes for participants to complete. No participant took significantly longer than this to complete the test;

Test scoring: Scores were out of 60, however, answers were adjusted to consider date of birth as it has been shown that scores increase with younger generations.

3.3.2 Edinburgh handedness inventory

The Edinburgh Handedness Inventory (Oldfield, 1971) is a simple questionnaire with 12 questions developed to assess hand preference. The participant is asked to state when answering each question whether they have a preference is to use the left or the right hand or foot. Participants are allowed to differentiate between simple 'preference' of using left or right, whether they would never consider using the opposite limb (considered a strong preference) or whether they felt indifferent (could use either left or right). If the participant had no experience in relation to a particular question, they were allowed to leave that question blank.

Task scoring: Each questionnaire was scored according to guidance form (Oldfield, 1971). Raw scores ranged between -100 to +100. Scores of above 40 indicated a right-handed preference. Scores of 39 and below indicated either ambidextrous or left-handed preferences.

3.3.3 Mini mental state exam

The Mini Mental State Exam (MMSE) is a 30 point questionnaire, originally published in 1975 by (Folstein, Folstein, & McHugh, 1975) and has since become a widely accepted method of assessing the basic cognitive abilities of patients and in particular to identify any memory or cognitive impairments. It can be used to highlight the possibility of Mild Cognitive Impairment (a

score of below 24) and also the level of deterioration in memory and cognitive abilities in dementia patients over time. For a copy of the questionnaire used for the study see Appendix E.

3.3.4 Cambridge brain sciences

The Cambridge brain sciences (CBS) website at the time of data collection contained 14 different online tasks that measure 4 broad functions; memory (4 tests), reasoning (4 tests), concentration (3 tests) and planning (3 tests). Of these 6 tests were selected to be part of this study battery; color-word remapping, feature match, paired associates, self-ordered search, spatial planning and spatial span.

In collaboration with Adam Hampshire, a web-based user interface was set up for this study specifically. A closed web url* used for this study, as opposed to the public website: http://www.cambridgebrainsciences.com. Usernames were created up for each participant based on their unique identifier number. The participants were introduced to the website. The operator asked the participant if they were comfortable using a mouse and if they required some direction or a brief practice, this was provided. The tasks were run one after the other in a set order. At the start of each task, the computer screen provided instructions which the operator read aloud, or the participant read to themselves (at the preference of the participant). Exact wording of the instructions can be found in Appendix E. When the instructions had been read, the participant was asked to begin by clicking on a 'start' button on the screen with their mouse. Each task lasted for approximately 2 - 3 minutes. Population mean scores for all tasks can be found in table 9. The spatial planning task used for this study was an adaptation of the one used in (Hampshire et al., 2012) so mean scores from this study do not equate.

Colour-word remapping: This is based on the Stroop phenomenon (Stroop, 1935) demonstrating that 'interference' in information processing cause delays in response to a given stimuli. During the task, participants are shown three words, one at the top, and two below, in boxes side by side. The participants are asked to choose the box that represents the colour of the ink, (as opposed to its spelling) what the word at the top of the screen is written in. The participant is asked to answer as many trials as they can in 90 seconds (Fig. 32).

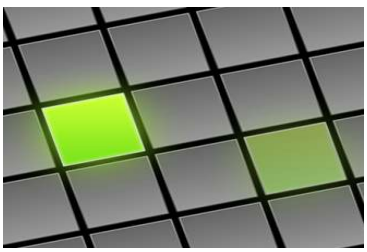
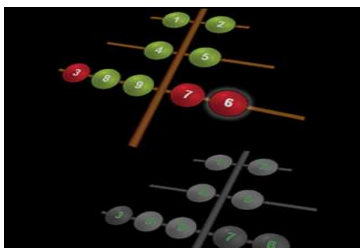
Scoring of the task: If the participant answers correctly, they gain a point, if they answer incorrectly, they lose a point. Final scores can be negative.

Spatial span: This task is based on the established 'Corsi Block Tapping' task (1972) and used to assess visuospatial working memory. For this task, the participant is shown an empty grid (25 squares, 5 x 5). After a beep, a series of squares light up one by one. After these squares have lit up, the grid is returned to its blank status, and the participant is asked to copy the sequence of squares in the order that they were lit up by pressing the respective boxes. For the first trial, only 3 squares are lit up. If the participant gets that right, the next task has one additional square in the sequence. If the participant gets the task wrong, the number of squares is reduced (Fig. 32).

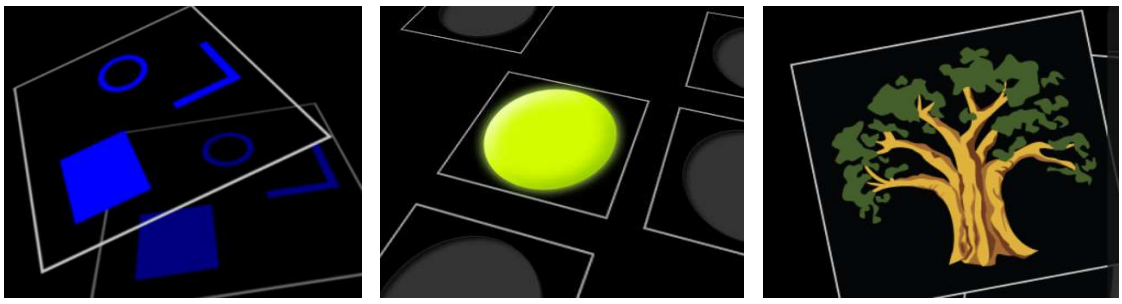
Scoring of the task: The highest score a participant achieves (i.e. the longest sequence of squares they can remember) and their mean scores are calculated. It is possible to get 0 as a score if no trials are answered correctly.

Feature match: This task measures visual attention; the ability to focus on a complex visual pattern. During the task, two boxes with a complex array of visual shapes were shown on the screen. The participant was asked to select from two button's; either 'match' to indicate the two squares contain exactly the same pattern of objects, or 'mismatch' to indicate there was some difference between the two. The task lasted 90 seconds and the participant was asked to complete as many trials as possible in this time (Fig. 32).

Scoring of the task: The task scored by adding or subtracting a point depending on correct or incorrect answers; Participant had to answer as many as possible in 90 seconds. Outcome measure = Total score.

Color word remapping | Spatial span | Spatial planning



Feature match/Visual attention | Self-ordered search | Paired associates

Figure 32 Illustrations of selected Cambridge Brain Sciences tasks

Spatial Planning: Also known as the Hampshire Tree task. This task is based on the Tower of London task (Shallice, 1982). The Tower of London task has been shown to be sensitive to frontal lobe Damage. It is frequently used to assess planning and problem-solving abilities. This adaptation is a timed task (3 minutes) that contains an image of a stylised 'tree' with six branches, three on the left, three on the right. Each branch holds a number of 'beads'. The top branches hold only one bead each, the second branches hold two beads each and the lowest branches hold three beads. Each bead is numbered. At the start of a task, beads are found on the tree in a random order. The participant is asked to rearrange these beads in ascending order, starting from '1' top right to the highest value bottom left. The participant is asked to try and solve as many problems as possible in the given time frame (Fig. 32).

Scoring of the task: The task is timed (3 minutes); The degree of difficulty increases incrementally; Trials are aborted if more than twice the number of moves needed to answer the task are attempted; The total score increased incrementally using the following formula:

(Minimum number of moves required) x 2 – (number of moves actually made).

Paired associates: Variants of this task are used to assess memory impairments in aging clinical populations (Gould et al., 2005; Gould, Brown, Owen, Ffytche, & Howard, 2003). For this task, boxes appear with a different object inside each box. The boxes are shown one by one and then a cover is placed over them so the contents cannot be seen. A new open box with an object that matches one of the covered boxes appears. The participant is asked to click on the covered box they think the matching object is hidden in. If the participant remembers the contents correctly,

the next trial will have one more box to remember. If the participant fails the trial, the next one will have one less box. After 3 errors, the test ends (Fig. 32).

Scoring of the task: Task is scored by increasing or decreasing by 1 point depending on success of each trial.

Spatial working memory: This task measures planning, organisation and memory function. It is based on a task to assess search strategy behaviour (Collins et al., 1998). A set of blank boxes appear on the screen. The participant is asked to click on boxes to find a token. There are several rules that the participant must comply with in order to succeed in the trail. They are not allowed to click on an empty box twice; they are not allowed to re-click on a box if a token has already been found there. Once a token has been found in every box presented, a new trial will commence. If three errors in total are made, the test ends (Fig. 32).

Scoring of the task: The maximum number of tokens found, and the average number of tokens found across trials are provided as scores. Number of errors are also recorded.

Below are four tables describing the following measures relevant to the tests used in this study from (Hampshire et al., 2012): Table 6 gives an overview of test-retest reliabilities using data acquired from the general public cohort. Table 7 gives relevant measures from the first study identifying task loadings that aligned either to brain activation networks of ‘working memory’ or ‘reasoning’. Table 8 gives measures of task loadings from the second PCA analysis identifying three components, ‘short term memory’, ‘reasoning’ and ‘verbal’. Tables 9 and 10 provide population and sample means respectively.

Table 6 Test-retest reliabilities (Hampshire, 2012)

	N	Retest reliability (Pearson's correlation)
Spatial span	647	0.62
Self-ordered search	1113	0.66
Paired associates	1131	0.45
Spatial planning	1150	0.87
Feature match	1132	0.57
Color-word remapping	1151	0.92

Table 7 PCA of fMRI activation levels from performance of 6 cognitive tasks (Hampshire, 2012)

	MD wm	MD r
Spatial span	0.86	0.17
Self-ordered search	0.69	0.38
Paired associates	0.62	0.56
Spatial planning	0.50	0.58
Feature match	0.49	0.68
Color-word remapping	0.42	0.69

Table 8 Task-component loadings extracted from PCA results of internet data (Hampshire, 2012)

	1 STM	2 Reasoning	3 Verbal
Spatial span	**0.69**	0.22	
Self-ordered search	**0.62**	0.16	
Paired associates	**0.58**		0.25
Spatial planning	0.41	**0.45**	
Feature match	0.15	**0.57**	0.22
Color-word remapping	0.22	0.35	**0.51**

Table 9 Population means scores and factor scores of tasks (Hampshire, 2012)

	Mean	SD	STM	Reasoning	Verbal
Color-word remapping	30.92	13.01			0.51
Feature match	131.35	32.79		0.66	
Paired associates	5.28	1.13	0.58		
Self-ordered search	8.23	2.10	0.62		
Spatial planning	64	10.185	0.41	0.45	
Spatial span	6.15	1.07	0.69		

Table 10 Study sample (86 participants) mean scores

	Mean	SD
Color-word remapping	22.27	14.57
Feature match	119.70	32.52
Paired associates	4.71	1.09
Self-ordered search	7.34	1.10
Spatial planning*	18.74	8.34
Spatial span	5.49	1.13

*Spatial planning task is a different version from the one included in Hampshire et al, 2012 and therefore means are not comparable.

3.4 Neuroimaging acquisition

3.4.1 Principles of magnetic resonance imaging

All biological tissue is ultimately composed of molecules made up of atoms, formed from various combinations of protons, electrons and neutrons. Magnetic Resonance Imaging (MRI) focuses on the behaviour of protons in biological tissue. It uses a strong magnetic field to align protons (usually hydrogen protons within water molecules) in living tissue along a single axis. A radio frequency pulse is then emitted from the MRI scanner which excites these protons. After a short period of frenzy, the protons relax and in doing so produce a small radio frequency signal of their own.

Different types of tissues have different densities of protons and produce different types of signal. For example, fatty tissues produce a different signal compared to tissues with higher water

content. These signals are picked up and depending on their signature and location are transformed into a three-dimensional image.

3.4.1.1 Diffusion weighted imaging and the diffusion tensor

Diffusion weighted imaging examines an additional form of proton or molecule behaviour. It is based upon the assumption that water molecules when unimpeded travel randomly in different directions over time. (Beaulieu, 2002) calls this the 'random walk' (Fig. 33). DWI uses certain temporal patterns of RF pulses to gather information about how far the molecules have travelled over a short period of time. The use of different gradients of magnetic fields positioned within the scanner create a three-dimensional mesh or grid across which these molecular walks are measured.

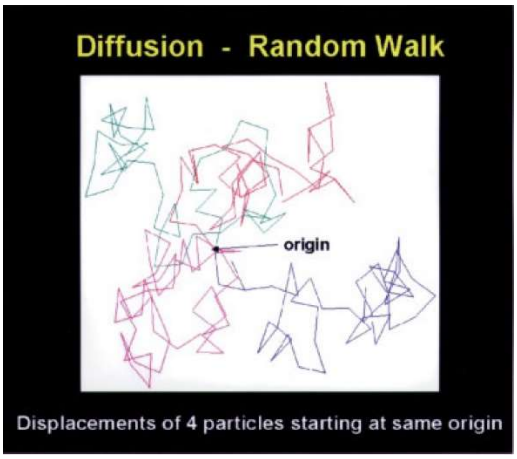


Figure 33 The random walk (Beaulieu 2002)

Depending on where in the brain the water molecules are, different patterns of diffusion (the distance molecules travel over time and the direction they travel) can be identified. Water within cerebro-spinal fluid of the ventricles for example is relatively unimpeded and so is able to diffuse naturally in a random direction and for relatively long distances. Water within long narrow structures like neuron axons, enclosed in cellular membranes and further wrapped in a myelin sheaths demonstrate restricted diffusion and exhibits a favoured direction of travel (i.e. along the axon rather than across it) (Fig. 34).

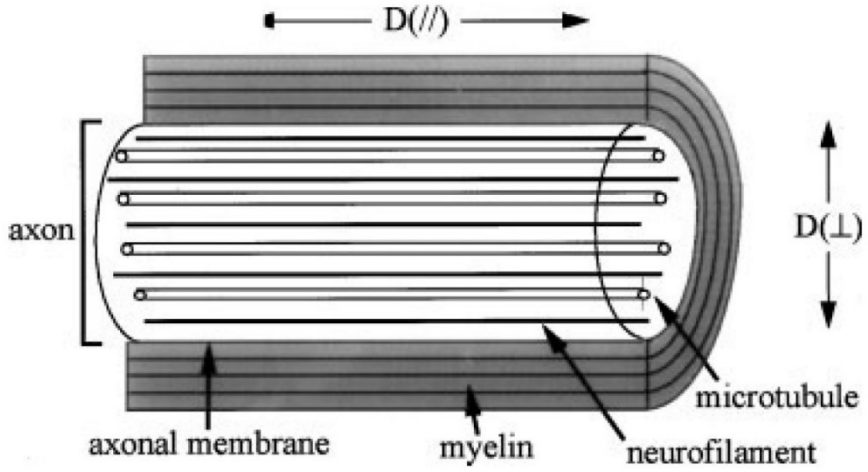


Figure 34 Section of axon illustrating the structural restrictions to water molecule movement (Beaulieu 2002)

Free random movement of water molecules is termed ‘isotropic’ in nature, whereas restricted movement along a particular axis or direction is termed ‘anisotropic’. Axons travelling together to form bundles of white matter pathways or tracts tend to exhibit an anisotropic signature.

Diffusion *weighted* imaging convert’s information about the different levels of movement or diffusion of water into a corresponding shade of grey for each voxel.

Diffusion *Tensor* Imaging combines information about the direction water molecules flow in along with the distance they travel to generate a diffusion tensor or ellipsoid for each voxel. The tensor uses a combination of eigen vectors and eigen values organised in the form of a matrix which can be visualised as a ‘tensor’ (one tensor per voxel) to represent the average direction that the aggregated water molecules travelled in (see Fig 35 and 36).

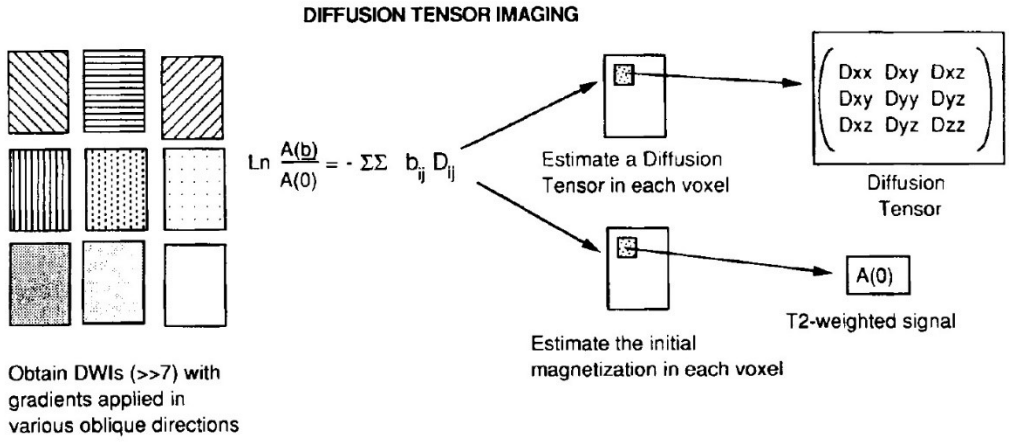


Figure 35 The difference between DWI and DTI (Basser, 1995)

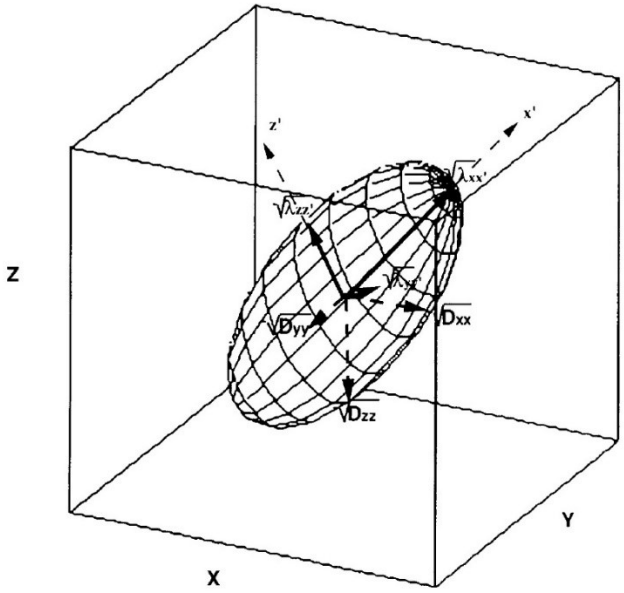


Figure 36 Diffusion ellipsoid, (Basser 1995)

3.4.1.2 Diffusion tensor imaging

Each diffusion tensor is compared with its neighbour. If it contains similar properties in terms of direction (within a certain angle threshold) these tensors/voxels join together to form a path or pathway (see Fig 37).

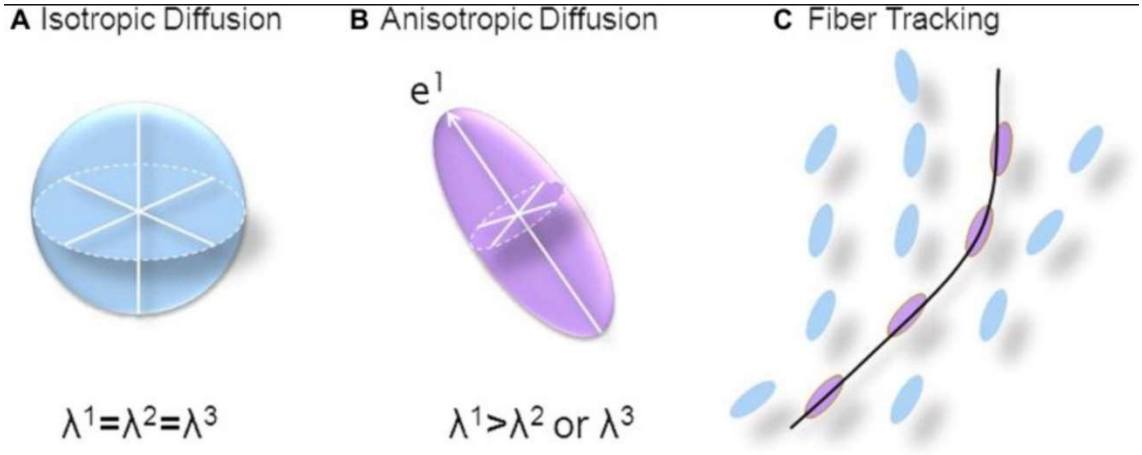


Figure 37 Connection of neighbouring voxels with similar directionality to form a streamline (Lerner 2003)

Software packages use algorithms to 'reconstruct' these virtual pathways across the entire brain. Once whole brain tractography has been completed, regions of interest can be drawn onto 2D maps. These instruct the program to isolate a set of streamlines or virtual 'fibres' traveling through certain regions of the brain from other pathways. Metrics from these delineated pathways are then extracted for further scrutiny. Indices such as mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD) can be extracted to provide inferred information regarding the microstructure of the reconstructed fibre bundles.

There are limits however to DTI methods. In DTI a single diffusion tensor provides information about the averaged water diffusivity and direction of all axons within a single voxel. A voxel represents a relatively large space in terms of brain microstructure. While a voxel is a few millimetres wide, the average axon diameter is only microns wide. A voxel can contain inferred information from potentially hundreds of thousands of individual axons. This means that at many points in the brain a voxel may be representing more than just one bundle of axons travelling together in the same direction and in many instances different fibre bundles may be travelling in different directions or potentially crossing paths entirely. With a single tensor the average of all these data can mask true structure.

3.4.1.3 High Angular Resolution Diffusion Imaging (HARDI)

HARDI acquisition sequences differ from classic DWI sequences by increasing the number of diffusion weighting directions measured (as well as altering other parameters such as the b-

value). This enables more information about the possible different direction's fibre bundles may be travelling in within a voxel to be extracted.

3.4.1.4 Spherical Deconvolution

Spherical Deconvolution is a method that extracts information on the distribution of fibre orientations within each voxel. A mathematical model called the Fibre Response Function (FRF) described by (Anderson, 2005; Tournier et al., 2004) is used to unpack or 'deconvolve' signal information allocated to each voxel. It does this by estimating the weight of different fibre bundles travelling in different directions within a voxel and comparing this information to the total diffusion signal across the voxel. The result is the Fibre Orientation Distribution (FOD). The FOD can be illustrated by a spherical shape that is morphed into different peaks or 'lobes' according to the weighted directions of fibre bundles (Fig. 38) distributed within that region (Dell'Acqua et al., 2013).

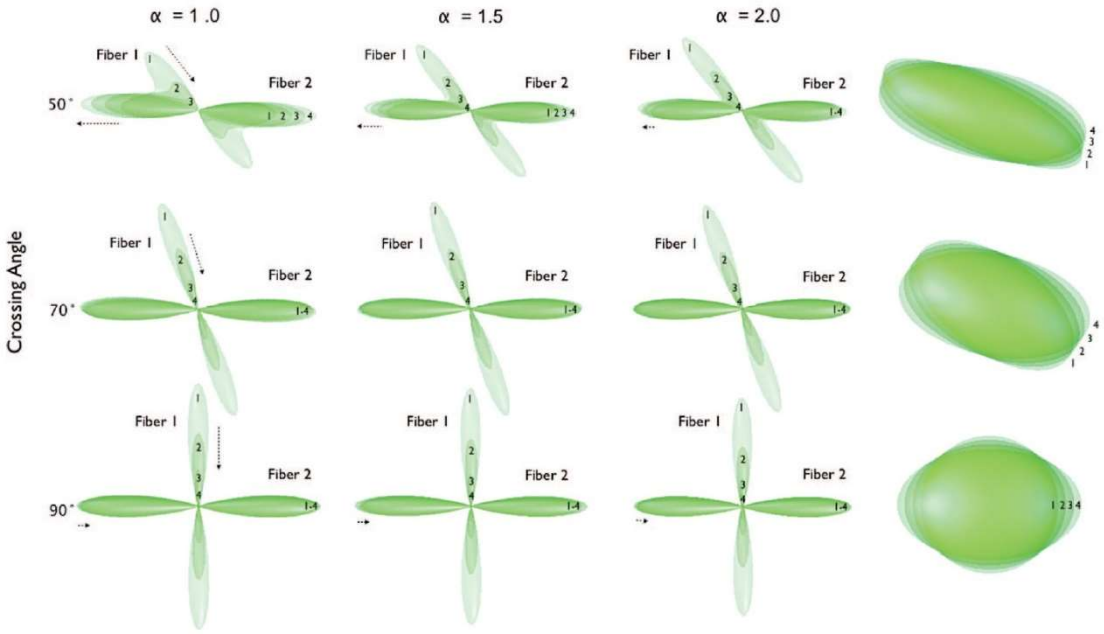


Figure 38 Comparison between SD and Diffusion Tensor when two fibres are crossing within one voxel (Dell Acqua, 2012)

3.4.1.5 Hindrance Modulated Orientation Anisotropy

From Spherical Deconvolution methods an index called Hindrance Modulated Orientation Anisotropy (HMOA) to provide information about the characteristics of individual fibre bundles. HMOA represents the absolute amplitude of each FOD lobe. The HMOA index cannot be directly

compared with FA or MD as it combines information regarding certain diffusivity properties (including radial diffusion hindrance) and the directionality (anisotropy) of the tissue.

Simulations run by (Dell'Acqua et al., 2013) demonstrated that HMOA was more sensitive than MD and FA when alterations to radial diffusivity and axonal radius were modelled. HMOA decreased as both these parameters increased at an earlier and steeper degree compared to the traditional indices.

In addition to increased sensitivity to some microstructural changes, Figure 39 illustrates the increased granularity provided by using this method. At the intersection of crossing fibres of the arcuate and corpus callosum for example, DTI methods using fractional anisotropy provide a merged average of the two fibre bundle directions, whereas the hindrance modulated orientation aniostropy provides much clearer distinction between these proximal but separate bundles.

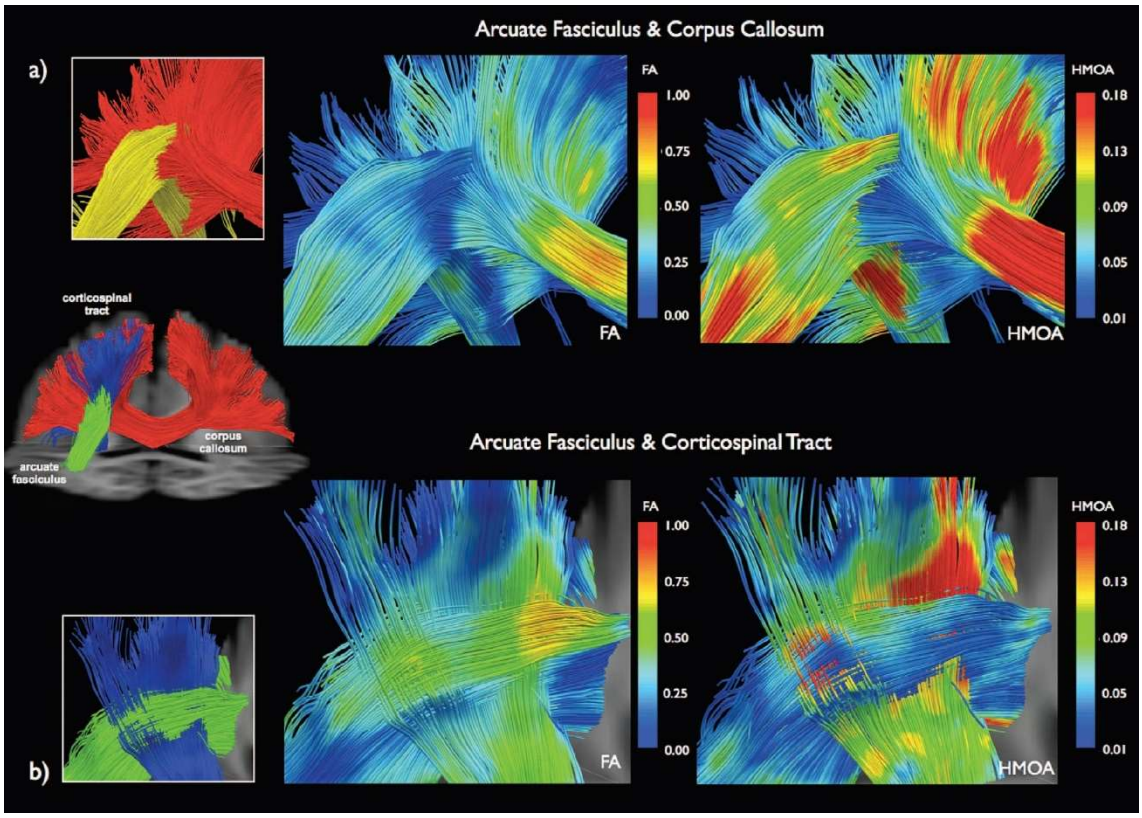


Figure 39 DTI and SD techniques compared (Dell Acqua 2012)

3.4.2 MRI safety training

All research team members involved in recruitment and supervision of MRI scans attended MRI safety training conducted by the Centre for Neuroimaging Sciences.

3.4.3 HARDI acquisition

A 3T General Electric Signa HDx twinSpeed system MRI scanner (General Electric, Milwaukee, WI, USA) with an 8 channel head coil was used to collect the data. A spin-echo EPI sequence with cardiac gating was applied with TR of 20/30 R-R intervals. Rostro-caudal phase encoding was applied. 60 contiguous near-axial slices were acquired. 60 diffusion-weighted directions and 7 non-diffusion-weighted volumes with an echo time of 93.4 ms were used. A b-value of 3000 s/mm2 was applied. Voxel size was 2.4 x 2.4 x 2.4 mm, matrix 128x128, and FOV 307 x 307 mm.

3.4.4 Data pre-processing

Raw Dicom files were converted to Nifti. Each DWI scan acquisition file contains 60 DWI images and 7 B0 images. The files were re-ordered using Explore DTI (Leemans, Jeurissen, Sijbers, & Jones, 2009) so that all B0 images were placed together at the start of the file sequence.

Files were then visually inspected using FSL (version 3.1.8) (Smith et al., 2004) using orthographic and lightbox views. DWI volumes were set a maximum brightness value of 500. All 60 axial slices per volume/image in lightbox view were examined. Any slice that displayed an artefact, image quality issue or potential anatomical abnormality was described and assigned a pass or fail category.

All accepted scans were then corrected for head motion and eddy current distortion using Explore DTI software. A mask was applied to each scan to remove the skull from the image. The b-matrix for each subject was then re-oriented as to enable better estimation of diffusion tensor orientations (Leemans et al., 2009).

Spherical Deconvolution was applied using the software StarTrack (www.natbrainlab.com) which incorporated the damped version of the Richardson-Lucy algorithm described by (Dell'Acqua et al., 2010). For the smaller data set described in Chapter 4 the following parameters were set: Fibre response parameter α = 1.2. 200 algorithm iterations. ALFA = 1.2, Alg.Type = 2. nn =

0.00145, rr = 16, LM parameters: abs = 0.00145. Angle threshold = 35; ABS threshold 0.002. Step size = 0.5. Min length = 20, Max length = 300. Algorithm type = 1 (1 – M-Euler, 2 – M-FACT).

For the larger data set described in 5 the following updated parameters were set: Fibre response parameter α = 1.5. 200 algorithm iterations. ALFA = 1.5. Alg.Type = 2. nn = 0.0015. rr = 15. LM parameters: abs = 0.0015. Angle threshold = 35. ABS threshold = 0.0025. Step Size = 1. Min Length = 20, Algorithm Type = 2 (1=M-FACT, 2=M-Euler).

3.5 Tractography

Whole brain tractography was applied to the datasets using the software StarTrack (www.natbrainlab.com). To ensure good definition of crossing tracks within voxels a classical Euler algorithm was used (Dell'Acqua, Simmons, Williams, & Catani, 2012). Fibre orientation estimates were obtained by selecting the orientation corresponding to the peaks (local maxima) of the Fibre Orientation Density (FOD) profiles. Absolute and relative thresholds on the FOD amplitude were applied to exclude spurious FOD peaks (Dell'Acqua et al., 2012).

3.5.1 Tract dissection software

All tracts were delineated using TrackVis software (Version 0.6.1, build 2017.01.18) freely available from: http://www.trackvis.org/ . A full description of all manual and semi-automated dissection protocols can be found in Appendix F. The reliability of these dissection protocols is reported in Chapter 4.

3.5.2 Manual dissection method

A full description of manual dissection methods used can be found in Chapter 4 and Appendix F.

3.5.3 Semi-automated dissection method: Megatrack

Megatrack is a software designed to reduce the amount of time conducting dissections across large data sets whilst still maintaining accuracy and reliability. There are several tools available that automate tractography already, but these tend to be limited in that once the full data set has been produced there is often no opportunity for tracts to be checked and amended if artefacts are evident on an individual by individual basis. The way Megatrack works is by combining tracts

from each individual within a dataset into one merged dataset. This merged dataset is then dissected manually one single time as per expert anatomical protocols. This single set of ROIs produced on the consolidated data set is then split out and applied to each individual's whole brain tract automatically. Indices such as tract volume and Hindrance Modulated Orientation Anisotropy (HMOA) are extracted for each individual and made available in the form of an excel spreadsheet for further analysis. It is possible to access individual tract dissections for all individuals once they have been propagated across the whole data set. However, at the time of writing this information was unavailable. Detailed descriptions of the manual and semi-automated protocols are found in Appendix F.

3.6 Analysis

All analysis was conducted in SPSS 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

3.6.1 Dissection protocol reliability

Mean volumes and HMOA values were extracted for each tract for the whole group and for younger and older adult subgroups. Independent samples T tests were run to compare volume and HMOA values between younger and older adults.

For manual dissection protocol reliability assessment, the volume and HMOA values for each tract for both rounds were compared using Intra-class Correlation Coefficient (ICC) analysis. A two-way mixed, absolute agreement model with 95% Confidence Interval was selected. ICC tests were run on each group as a whole, and then for young and older adult subgroups separately.

To compare manual protocols with the semi-automated process two approaches were used. A two-way mixed, consistency, 95% CI model of Intra-class correlation coefficient (ICC) analysis was used to assess reliability between round 1 of the manual dissection and the semi-automated method. Then Bland Altman plots (Bland & Altman, 1986) were generated to illustrate levels of agreement between round 1 manual and semi-automated methods. Paired T-tests were run to identify any significant bias between methods.

3.6.2 Data preparation for age, cognitive and tract microstructure measures

Task performance score were standardized by conversion to z scores. Shapiro-Wilk tests were used to verify normality of age, behavioural and anatomical variables. Age was positively skewed. A log transformation was conducted, and these data were used for subsequent analysis. HMOA of the third and fourth segments of the corpus callosum and the right uncinate had significantly non normal distributed data. These data were Log10 transformed for and used for subsequent analysis. spatial planning and spatial span tasks were observed to have a slight positive skew. The paired associates, self-ordered search and the short-term memory component all exhibited slight negative skew. Transformations were unsuccessful in producing a normal distribution. For

these tasks it was decided to leave these data without transformation due to the robust nature of the analytical methods used.

To align neuropsychological measures together, z scores from each individual task were used in analysis. Z scores from three tasks (paired associates, self-ordered search and spatial span), were grouped together into an aggregated metric representing the short term memory factor identified by (Hampshire et al., 2012). The following equation was used to do this:

Short term memory component = ((spatial span x 0.69) + (paired associates x 0.58) + (self-ordered search * 0.62))

3.6.3 Regression and correlation analysis for research questions

For each of the three research questions a mediation model was proposed to identify indirect effects that changes to microstructure in tracts of interest may have on age related cognitive decline. For each cognitive task assessed, tracts of interest were identified as relevant to the cognitive task from the literature. For research question one examining selective attention, the left and right cingulum were identified. For research questions two and three, examining spatial working memory and planning ability, the same 5 tracts were identified; the cingulum, IFOF and the three tracts of the SLF system (SLFI, II and III). Tracts from both hemispheres were included, 10 tracts in total.

A structured set of preliminary tests were applied to identify the strongest candidate tracts from the wider group for each cognitive task to be included in the mediation analysis. These tests were organised in line with list of conditions required to identify an indirect (mediation) effect (Baron & Kenny, 1986) as follows:

- To test for a significant relationship between age and cognition, regression analysis was conducted between age as the predictor variable and task performance scores as outcome variables.
- To test for a significant relationship(s) between age and tract microstructure, regression analysis were conducted with age set as the predictor variable and tract HMOA set as the outcome variable.

- To assess whether a significant relationship between tract HMOA and task performance was present, Pearson partial correlations were used to identify significant relationships between behavioural and anatomical variables correcting for handedness using the Edinburgh handedness questionnaire scores.

For all of these preliminary tests, significance was set at P value < 0.05. For research questions 2 & 3, a reasonably large number of tracts were included in the hypothesis, and appropriate Bonferroni corrections for multiple companions were applied as follows:

- For regression models of age and tract microstructure: Age (1 predictor variable) x 10 tracts (10 outcome variables): 0.05 / 10 = 0.005.
- For correlation tests between task performance (1 variable) and HMOA measures from 10 tracts (10 variables): 0.05 / 10 = 0.005.

3.6.4 Mediation analysis for research questions

In addition to verifying whether a change in significance occurred between the direct (outcome and predictor model) and indirect pathways (outcome, mediator and predictor model) as per (Baron & Kenny, 1986), we chose to also use measures of indirect effect using a bootstrap method so that we would be able to report the extent of mediation observed and potentially compare this across candidate tracts and cognitive tasks (Agler & De Boeck, 2017).

Mediation analysis was conducted using the macro 'PROCESS' for SPSS (Hayes, 2017). A bootstrap approach with bias-corrected accelerated confidence intervals (95%) using 1000 samples was used for statistical inference. This approach was selected at the time as it offered a more robust model for small to medium sample sizes. A separate mediation model was used for each candidate tract identified from the preliminary analysis per cognitive measure.

3.6.5 Exploratory analyses

The following additional measures were included in the exploratory analysis.

- HMOA of two frontal lobe tracts, the frontal aslant tract and the uncinate
- HMOA of the corpus callosum segmented into anterior, central and posterior sections.

- Performance scores for two further behavioural measures of executive function (feature match and self-ordered search) and a third task utilising both executive problem-solving processes and episodic memory (paired associates)

Regression analysis assessing age related declines in task performance and tract microstructure were conducted. Tests to assess correlations between all tracts and all tasks (outside of the original three research questions) were also run. Significance was set at P value <0.05. For appropriate combinations of tracts and tasks, mediation analyses were also conducted (as previously described).

Chapter 4 Methods Reliability of dissection protocols

4.1 Introduction

Manual tractography is now well established as a method to extract inferred information about white matter structures in the brain. However, the level of detail in the literature describing the delineation of these pathways is often limited and can vary considerably from research group to group. Focus on testing the reliability of these protocols tends also to be on a single age group (e.g. young healthy adults). Whilst the measurement of a protocol in one population sample is a useful exercise, it does perhaps suggest limitations for its application to a wider range of investigations.

The three examples of papers that assess intra-operator reliability of tract manual dissection protocols similar to those used in this thesis have examined reliability in young adults (Dini et al., 2013), older adults (Danielian, Iwata, Thomasson, & Floeter, 2010) and a small healthy/patient cohort of adults (Malykhin, Concha, Seres, Beaulieu, & Coupland, 2008; Yasmin et al., 2008). Varying levels of reliability were demonstrated. For example, dissection of the anterior segment of the corpus callosum produced excellent ICC scores for both FA and volume (Danielian et al., 2010). Whereas delineation of the uncinate produced volume ICC results ranging from 0.52 – 0.96, and FA results from 0.58 – 1.0 (Danielian et al., 2010; Dini et al., 2013; Malykhin et al., 2008; Yasmin et al., 2008). Similarly, the anterior section of the cingulum ranged from a tract volume ICC values of 0.35 – 0.78 (Malykhin et al., 2008). (Table 11).

Other papers have examined similar dissection protocols using different models of analysis, for example kappa (Wakana et al., 2007) or Coefficient of Variance. The former research group achieved a level of high overlap between tract positioning for 5 different tracts in a group of 10 healthy adults (mean age 26.1 ± 5.48 years). In the latter study of 17 healthy adults (mean age 39 ± 12 years) lower variability was found for microstructural measurements such as FA and MD, and slightly higher variability for tract volumes of the cortico-spinal tract (CST) and segments of the arcuate (Kristo et al., 2012).

Development of automated or semi-automated tractography methods has become more popular in the literature recently. Clear advantages to automated methods are the reduction to the amount

of time it takes to complete dissections especially across larger data sets. However, it's essential these methods are reliable. Several automated or semi-automated methods based on probabilistic tractography have been developed and tested against manual dissection protocols in healthy adults (Nucifora et al., 2012) and clinical populations (Hagler et al., 2009). For one probabilistic automated system called TRACULA (TRActs Constrained by UnderLying Anatomy) dissections on nine tracts or segments across both hemispheres were conducted on 33 healthy controls (mean age 42 ± 10) and 34 Schizophrenia patients (mean age 37 ± 10 years). This method used a set of healthy controls as a training data set initially then applied to a larger control group and patient group. TRACULA was able to identify significant differences between patient and control groups (Yendiki et al., 2011).

An alternative automated method also based on probabilistic principles found some systematic differences between methods depending on the tract being measured (Reich, Ozturk, Calabresi, & Mori, 2010). The automated method was sensitive enough to identify patient group differences in 27 healthy volunteers (mean age 33.2 ± 17.2 years) and 88 Multiple Sclerosis patients (mean age 46.4 ± 11.7 years) in the optic radiation, corpus callosum and CST but not the optic tract. This study highlights potential variation in agreement between methods according to the tract under observation. Also of interest is another probabilistic automated method applied across several different centers that was able differentiate tract specific indices between 58 older adult healthy controls (mean age 68.9 ± 5.8 years) and 45 patients with probable Alzheimer's Disease (mean age 72.8 ± 5.8 years) in the cingulum despite center effects (Fischer et al., 2012).

In this thesis, I have tested reliability of dissection methods for both manual and a new semi-automated dissection process using deterministic tractography. The dissection protocols are based on the Catani & Thiebaut de Schotten Atlas for tracts of interest (Catani & Thiebaut de Schotten, 2012). In an earlier Atlas (Catani & Thiebaut de Schotten, 2008) described high inter-rater correlation values across 10 different operators for volume (mean Pearson's r = 0.998, SD 0.001) and FA (mean r = 0.958, SD = 0.053). However, no data were provided for intra-rater reliability and so cannot be included for comparison. Therefore, I will document and test these adapted protocols to:

- Check that the established tract protocols are conducted to the standards already set in the literature (table 11).
- Assess the level of reliability and agreement between manual and the semi-automated dissection protocols.
- For pathways that have little information provided to date on their manual dissection reliability I will report my initial findings from both methods.
- Expand on the differences in reliability of both dissection protocols between young and older adults.

Other studies have investigated other parameters that contribute towards variation in dissection reliability such as scanner differences (Vollmar et al., 2010), acquisition sequence (Heiervang, Behrens, Mackay, Robson, & Johansen-Berg, 2006) and tractography algorithms (Ciccarelli et al., 2003). However, these are not relevant for this thesis as all these parameters were consistent for the current participant group.

Table 11 Dissection reliability reports from the literature

Tract	**Danielian**	**Dini**	**Malykhin**	**Volume range**	**FA range**
cingulum					
-Rostral			✓	0.35 – 0.78	0.87 – 0.89
-Dorsal			✓	0.82 – 0.84	0.85 – 0.90
-Parahipp			✓	0.86 – 0.87	0.85 – 0.95
corpus callosum –Ant	✓			0.96 – 0.99	0.99
IFOF		✓		0.72 – 0.77	0.83
uncinate	✓	✓	✓	0.52 – 0.96	0.58 – 1.0

corpus callosum segments 1&2 combined*

4.1.1 Reliability and agreement

The level of similarity between two sets of measurements can be quantified using Intraclass Correlation Coefficient (ICC) analysis. ICC values range from 0 to 1. A high ICC value (closer to 1) indicates that measurement errors are small. It has previously been suggested that while ICC scores cannot be interpreted in exactly the same way across different disciplines, a general rule of thumb could be that ICC values below 0.5 are poor, those between 0.5 and 0.75 demonstrate

moderate reliability scores between 0.75 and 0.9 are good and those over 0.9 represent excellent reliability (Koo & Li, 2016; Portney & Watkins, 2009).

An ICC model that assesses absolute agreement can be used to compare two sets of measurements made by the same operator on the same data set. An ICC model that examines consistency compares measurements made on the same data set but allows for any systematic errors between methods. ICC models with absolute agreement were applied to assess intra-rater reliability of manual dissection methods and those with consistency were applied to assess comparisons between manual and semi-automated methods that may include a systematic error (Bartlett & Frost, 2008). Bland Altman Plots (Bland & Altman, 1986) can provide additional information on any systematic errors or *bias* between methods (i.e. does one method consistently measure over or under the mean of the first method). Bland Altman plots were created when comparing manual and semi-automated methods (Appendix G).

4.2 Methods

4.2.1 Participants

A subset of participant who have scan only data was selected semi randomly (10 participants from a list assigned as young adults, 10 adults form a list assigned as 'older adults).

Table 12 Participant age and sex

Group (age range)	Sex (female, male)	Age Mean (SD)
Young adults (19 – 29 years)	5 (f), 4 (m)	24.89, (2.89)
Older adults (45 – 67 years)	4 (f), 5 (m)	52.22, (7.24)
Full group (19 – 67 years)	9 (f), 9 (m)	38.56 , (15.05)

4.2.2 Neuroimaging data preparation

For full details of neuroimaging data acquisition, pre-processing steps and tractography algorithms used for both manual and semi-automated methods see Chapter 3.

4.2.3 Manual dissection protocols

Manual dissections were conducted by one operator (AL) twice on each data set. For all tracts except for the IFOF and uncinate, the operator was blind to the age group of each participant. [for the IFOF and uncinate, the operator was blinded to the young adult age group but continued dissections for the older adults age group un-blinded (i.e. the operator was aware that participants belonged to the older age group although still blind to the exact age in years).

The dissection protocol for the cingulum was initially based on a single AND ROI approach using the axial slices for manual dissection protocol reliability analysis. However due to slightly different parameters applied to the Megatrack data set, which produced a higher level of artefacts for this particular tract, an updated two ROI approach was recommended and applied to the Megatrack data set instead. The dissection protocol for the FAT, IFOF, SLF and uncinate used a two AND ROI approach, using coronal slices. Some of the FAT and uncinate AND ROIs were spherical in shape rather than hand drawn flat regions. Dissection of the corpus callosum was conducted following the Witelson segmentation approach and used the sagittal slice to delineate the AND ROIs. Detailed descriptions of the anatomical landmarks used to position AND ROIs, and the logic used to position NOT ROIs for each tract are provided in individual tract dissection protocols found in Appendix F.

Merging of ROIs. Initial ICC results showed poor protocol reliability for both the rostrum and genu volumes. HMOA values were poor for the rostrum but excellent for the genu. Similarly, poor volume reliability results for the isthmus and splenium were observed (see table 13). The rostrum and genu and isthmus and splenium ROIs and tract data were merged and analysis re-run. Volume data was merged by adding the two tract volumes together. HMOA data was merged using the following equation:

$$((Tract1HMOA \times Tract1numStream) + (Tract2HMOA\_R \times Tract2numStream)) / (Tract1numStream + Tract2numStream)$$

[**numStream =** Number of streamlines for a particular tract]

4.2.4 Semi-automated dissection protocols

Megatrack is a new semi-automated dissection method that combines datasets from individuals into a single normalised (using a structural MNI template) 'mega' dataset. Delineation of regions of interest and creation of tracts is conducted on this 'mega' data set in a similar to the way one would perform dissections on a single data set (Dell'Acqua et al., 2015). Slight differences with the mega data set is that the tracts themselves are larger, as they contain an aggregate of all tracts across the whole data set (Fig. 40). There is a brief lag time when saving the Megatrack due to the larger size of the file. There are also more artefact fibres to be removed compared to the number that normally need to be removed from an individual data set. As with manual dissection methods ANDROI's and NOTROIs can be used. Spherical ROIs are not reproducible using Megatrack (for more details see user guide, Appendix F).

Once a tract has been delineated on the 'mega' data set, these parameters are applied to each individual data set and tract specific metrics are separated out and extracted for each individual. Developers of this new method have already published some preliminary results from testing of this process (Dell'Acqua et al., 2015). When comparing manual and Megatrack dissections of the arcuate in a group of 20 healthy subjects no statistical differences between methods were found in any of the measurements taken (volume, FA, MD, axial diffusivity and radial diffusivity). Megatrack has also been used in a recent study to explore connections from the sub genual cingulate region in a group 22 of healthy adults (aged between 20 – 40 years) (Vergani et al., 2016). However, at the date of writing a rigorous testing of this method against all of the matter tracts of interest relevant for this thesis had not yet been published.

The same operator completed dissections of the six association tracts (cingulum, IFOF, uncinate and six sub-tracts of the SLF system) and 1 intra lobar tract (FAT) in both hemispheres and 7 segments (initially) of the corpus callosum (a total of 21 separate tract/segments) using manual methods. For the semi-automated methods 19 tract/segments overall were dissected due to the merging of the first and second and sixth and seventh segments of the corpus callosum. The same dissection protocols were used for both methods apart from the following exceptions:

a) Sphere Regions of Interest cannot be drawn in Megatrack. Instead, a sphere was created from gradually increasing sizes of disk-shaped hand drawn ROIs to fit the parameters of a sphere.

b) The Megatrack data set is much larger and contains a vast number of streamlines. A larger number of NOT ROIs were required to remove all the visible artefacts in the Megatrack data set.

c) For the same reason, due to the large size of the average tract, some smaller artefacts may not have been visible to remove in the same way as with an individual data set.

A full description of the modified dissection protocols used for Megatrack can be found in Appendix F.

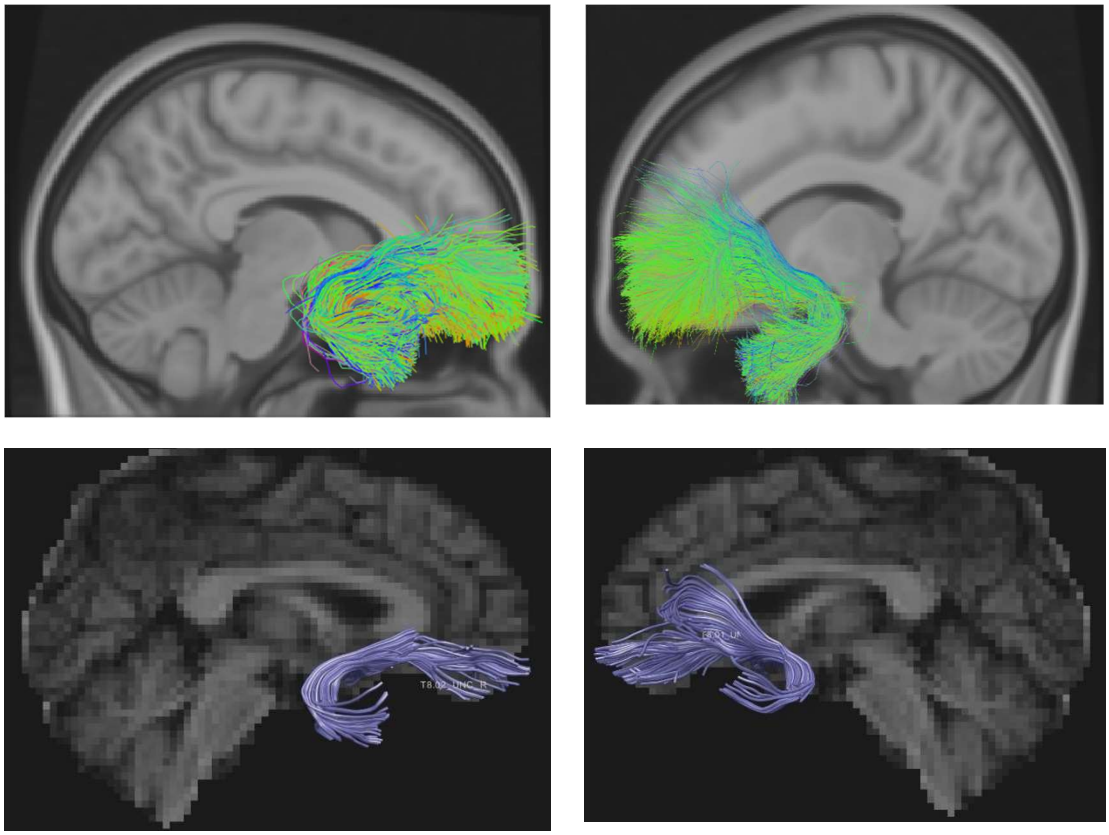


Figure 40 Megatrack (row 1) and individual manual dissection (row 2) of the uncinate

4.3 Analysis

All analysis was conducted using SPSS, version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). Mean volumes and HMOA values were extracted for each tract for the whole group and for younger and older adult subgroups. Independent samples T tests were run to compare volume and HMOA values between younger and older adults.

For manual dissection protocol reliability assessment, the volume and HMOA values for each tract for both rounds were compared using Intra-class Correlation Coefficient (ICC) analysis. A two-way mixed, absolute agreement model with 95% Confidence Interval was selected. ICC tests were run on each group as a whole, and then for young and older adult subgroups separately.

To compare manual protocols with the semi-automated process two approaches were used. A two-way mixed, consistency, 95% CI model of ICC analysis was used to assess how reliability between round 1 of the manual dissection and the semi-automated method. Then Bland Altman plots (Bland & Altman, 1986) were generated to illustrate levels of agreement between round 1 manual and semi-automated methods. Paired T-tests were run to identify any significant bias between methods.

4.4 Results

4.4.1 Mean volumes and HMOA values for each tract across whole group

Single association tract volumes ranged from 7.5ml (SD 4.91) for the left SLFII to 30.61ml (SD 6.37) for the left IFOF. The largest association tracts were the bilateral cingulum and bilateral IFOF which on measured over 30ml compared to the smaller association tracts like the right FAT, left SLFII and left SLFIII which were under 10 ml in volume. Association tracts HMOA ranged from 0.01 for the left SLFI to 0.02 for the bilateral IFOF.

The corpus callosum segment volumes ranged between 42.91 ml (SD 10.61) for CC4 and 119.26 ml (SD 21.23) for CC6&7 and were between 12.3 and 88.65 ml larger than the largest single association tract, the left IFOF. Corpus callosum segment HMOA values ranged from 0.021 (SD 0.003) for CC3 to 0.029 (SD 0.004) for CC6&7.

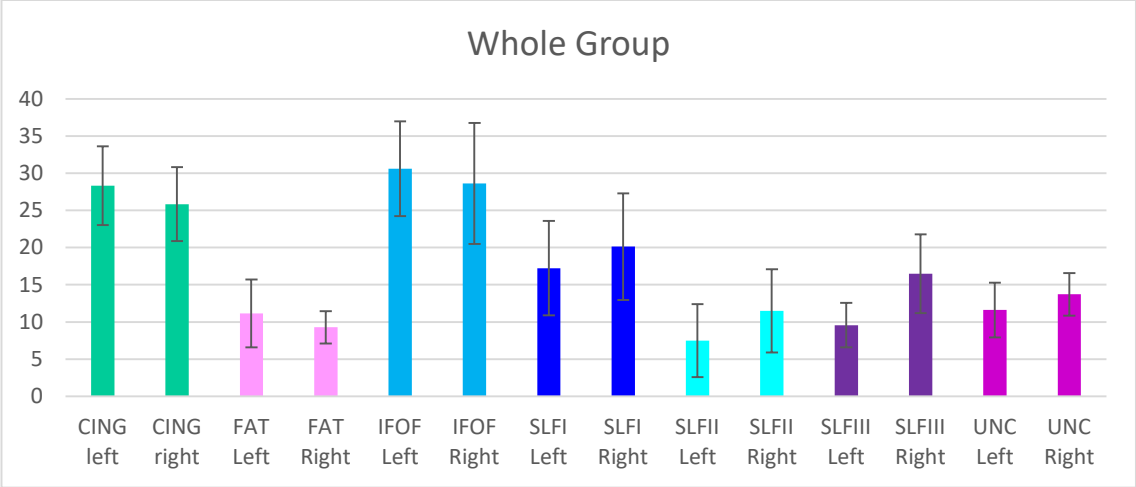


Figure 41 Mean tract volumes (ml) for association & intralobar tracts

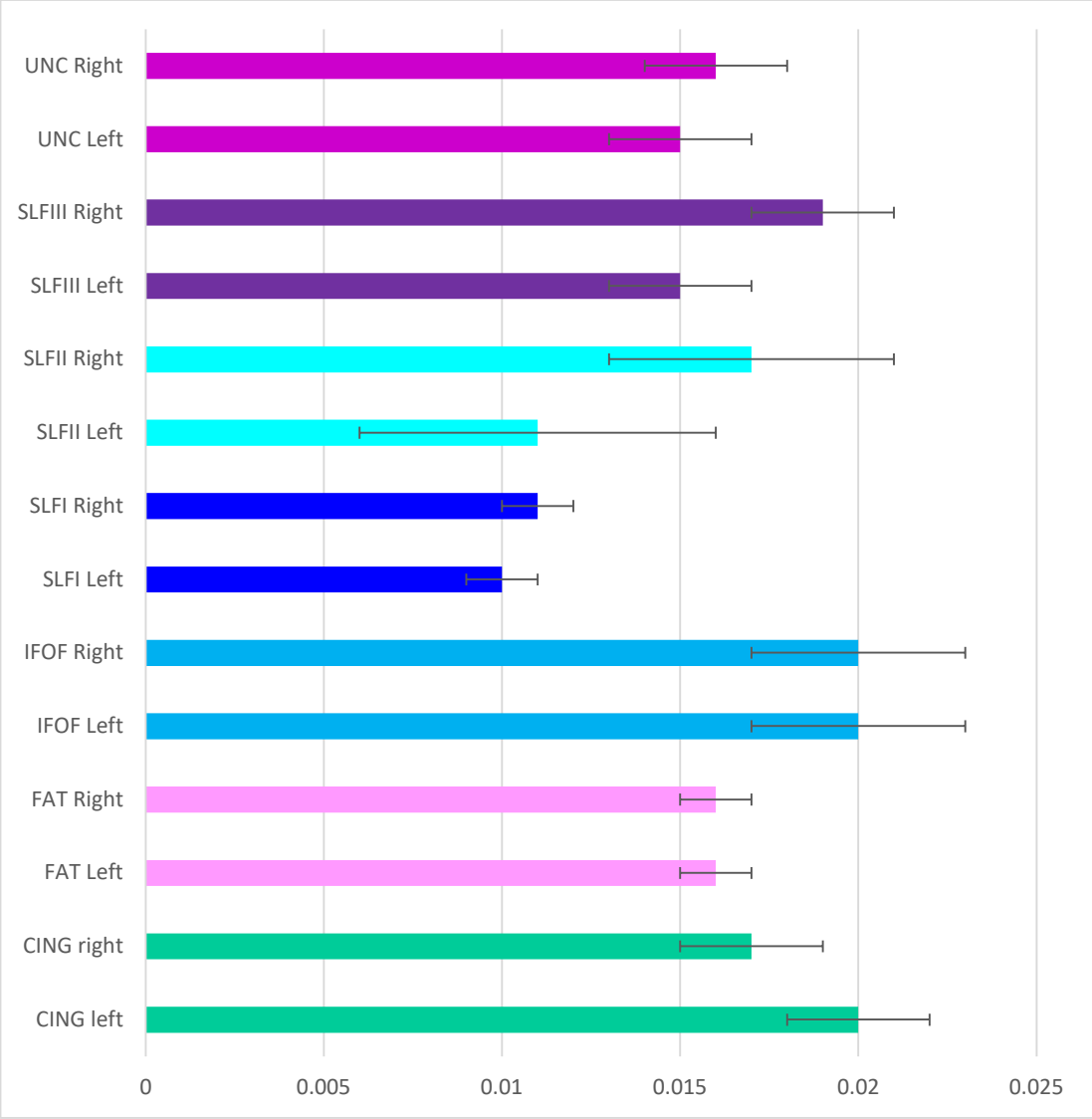


Figure 42 Mean tract HMOA for association & intralobar tracts

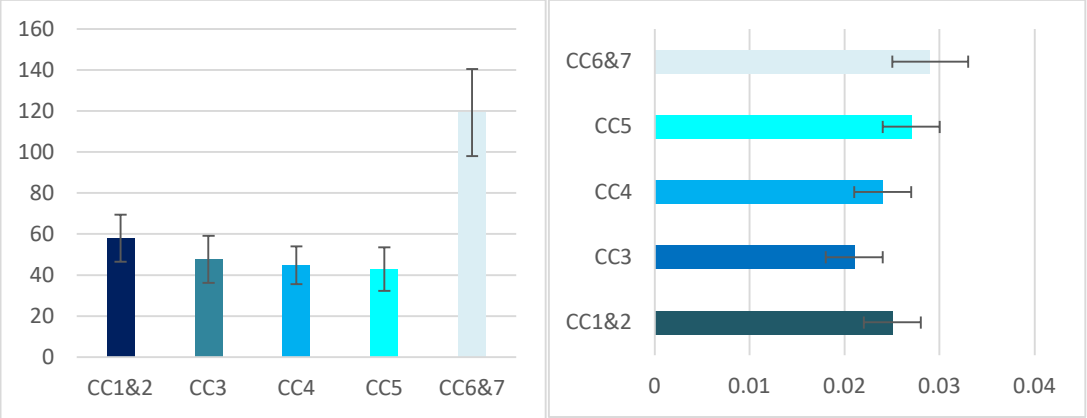


Figure 43 a) mean volume (ml) b) mean HMOA for segments of the corpus callosum

4.4.2 Between group differences

There was a significant reduction of volume in the older compared to the younger group in the left ($t = 2.71$, $p = 0.015$) and right ($t = 2.51$, $p = 0.023$) SLFIII HMOA (Fig. 44). There were no significant differences in HMOA between groups for any association tracts. There were no significant differences in volume between groups for any segments of the corpus callosum. However, there was a significant ($t = 2.25$, $p = 0.039$) reduction of HMOA in the older compared to the younger group for the first and second combined segments, the rostrum and genu (* represent sig difference between groups of < 0.05).

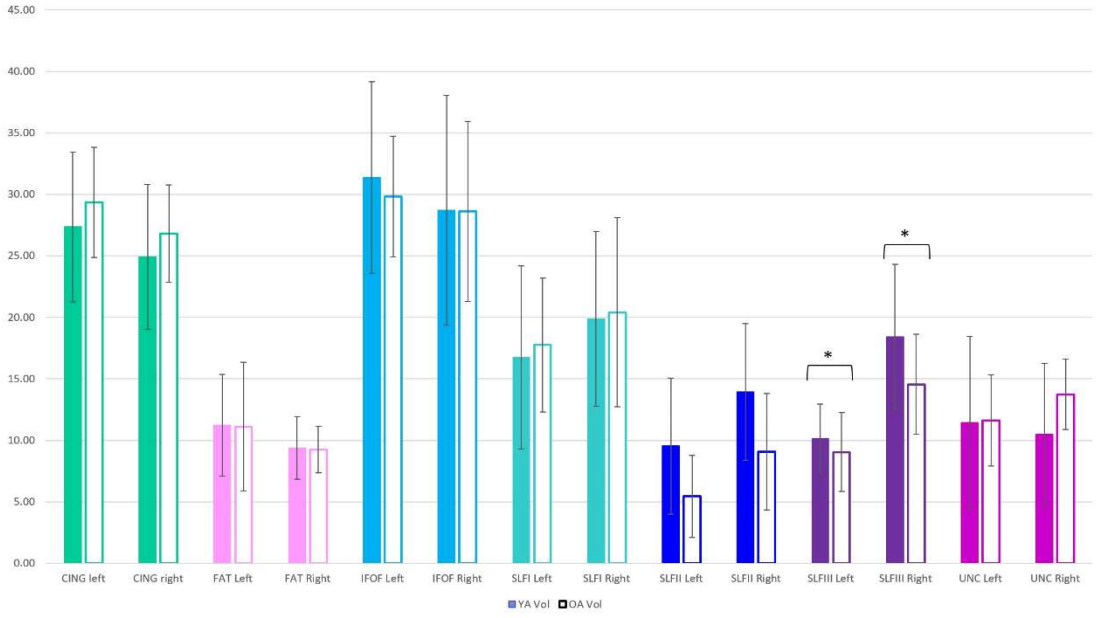


Figure 44 Mean association & intralobar tract volume (ml) between groups

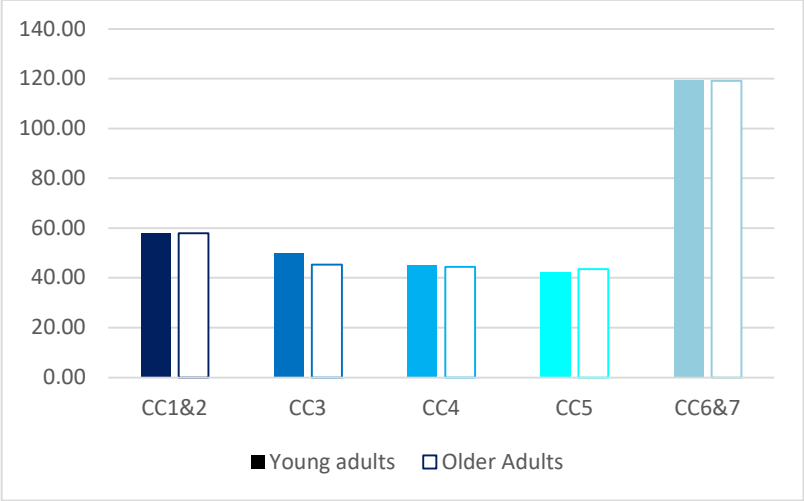


Figure 45 Mean corpus callosum segment volume (ml) between groups

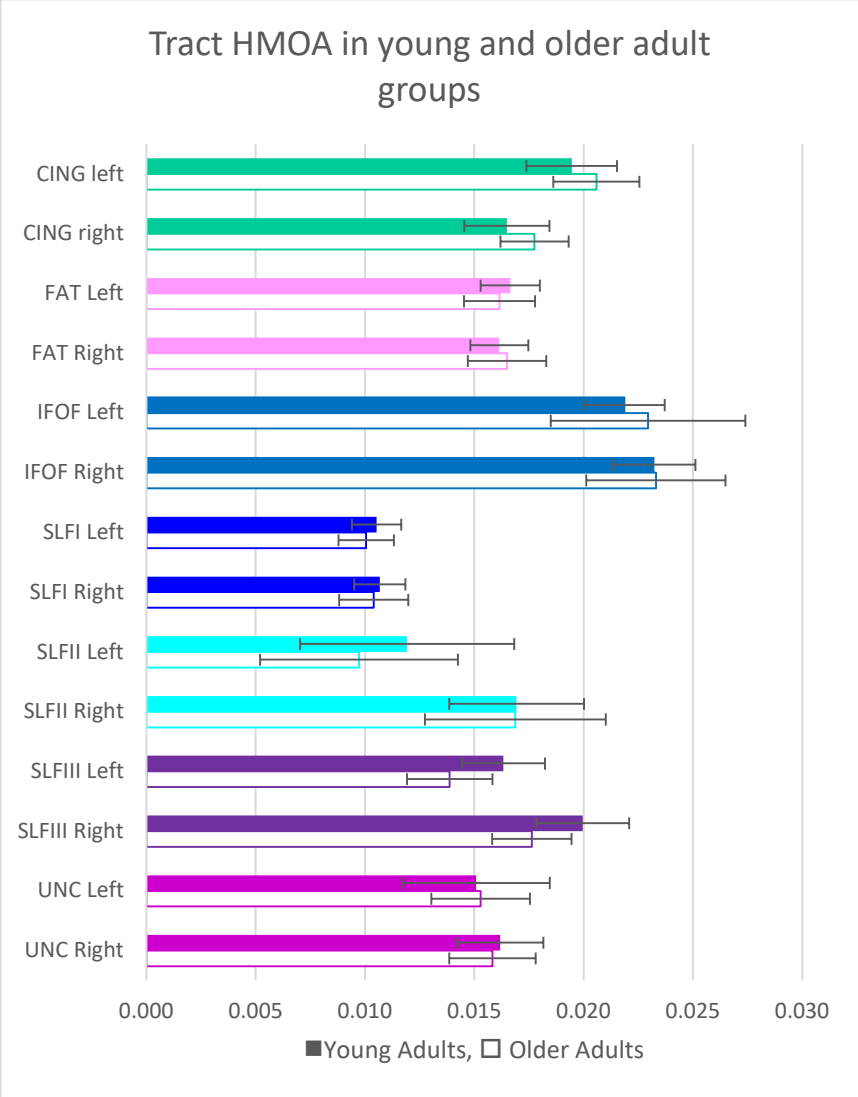


Figure 46 Mean association & intralobar tract HMOA between groups.

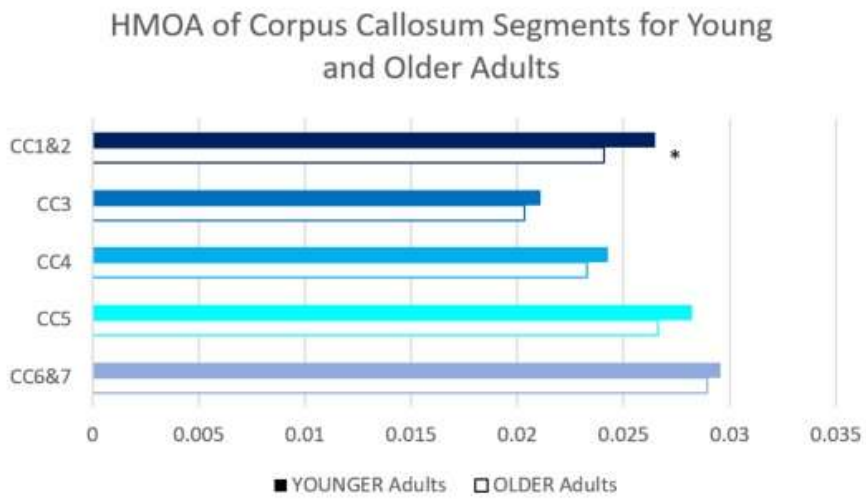


Figure 47 Mean HMOA of corpus callosum segments between groups.

4.4.3 Manual dissection protocol reliability

Intra-rater ICC's are presented in table 13. For tract volume across the whole group all tracts / segments achieved over 0.75 which is deemed good or excellent except for the first, second, third and sixth segments of the corpus callosum (CC1,0.510*, CC2, 0.558†, CC3,0.609†, CC6, 0.541†), the left SLFI (0.671†) and the right SLFIII (0.605†). In the young adult age group, all tract volumes achieved an ICC of < 0.75 except for segments 1, 6 and 7 of the corpus callosum (CC1,0.219, CC6 0.448*, CC7 0.650*), the left SLFI (0.633*) and the right SLFIII (0.544). In the older adult age group all tract volumes achieved an ICC of < 0.75 except for the left cingulum (0.651*), segment two, three and six of the corpus callosum (CC2 0.429, CC3 -0.104, CC6 0.661†), the right FAT, left IFOF, right SLFII and right SLF III (0.649*, 0.687*, 0.657*, 0.630*). Due to mainly poor reliability for first, second, sixth and seventh segments of the corpus callosum, segments 1 & 2 and segments 6 & 7 were merged for all subsequent analysis. After merging reliability improved for combined segments 1 & 2 (whole group 0.777†, young adults 0.829† and older adults 0.738* and so too for combined segments 6 & 7 (whole group 0.930†, young adults 0.942† and older adults 0.924†).

For HMOA all tracts except for the right SLFII (young adults 0.720*), right uncinate (young adults 0.683†) and the left SLFI (0.729*) achieved ICC scores of over 0.75.

Table 13 Manual dissection method ICC (two way mixed, 95% CI, absolute model) results

Tract (Segment)	***Volume***			***HMOA***		
	Young adults	Older Adults	Whole Group	Young adults	Older Adults	Whole Group
Left cingulum	**0.891†**	0.651*⇩	**0.805†**	**0.830†**	**0.859†⇧**	**0.854†**
Right cingulum	**0.951†**	**0.774*⇩**	**0.903†**	**0.959†**	**0.900†⇩**	**0.938†**
CC1 (1) (rostrum)	*0.219*	0.707*	0.510*	**0.910†**	*0.392*	0.502*
CC2 (2) (genu)	**0.855†**	*0.429*	0.558*	**0.963†**	**0.935†**	**0.951†**
CC (1&2)	0.738*	**0.829†⇧**	**0.777†**	**0.942†**	**0.973†⇧**	**0.973†**
CC (3) (rostral body)	**0.916†**	*-0.104⇩*	0.609†	**0.969†**	**0.990†⇧**	**0.982†**
CC (4) (anterior midbody)	**0.940†**	**0.760*⇩**	**0.866†**	**0.987†**	**0.966†⇩**	**0.979†**
CC (5) (posterior midbody)	**0.980†**	0.714*⇩	**0.852†**	**0.983†**	**0.961†⇩**	**0.978†**
CC6 (isthmus)	*0.488**	0.661†	0.541†	**0.881†**	**0.951†**	**0.914†**
CC7 (splenium)	0.650*	**0.853†**	**0.744†**	**0.977†**	**0.995†**	**0.985†**
CC (6&7)	**0.942†**	**0.924†⇩**	**0.930†**	**0.984†**	**0.995†⇧**	**0.990†**
Left FAT	**0.953†**	**0.965†⇧**	**0.957†**	**0.912†**	**0.962†⇧**	**0.939†**
Right FAT	**0.986†**	0.649*⇩	**0.797†**	**0.917†**	**0.944†⇧**	**0.933†**
Left IFOF	**0.964†**	0.687*⇩	**0.890†**	**0.995†**	**0.953†⇩**	**0.959†**
Right IFOF	**0.949†**	**0.806†⇩**	**0.901†**	**0.925†**	**0.919†⇩**	**0.916†**
Left SLFI	0.633*	**0.776†⇧**	0.671†	**0.788†**	0.729*⇩	**0.755†**
Right SLFI	**0.705***	**0.829†⇧**	**0.766†**	**0.811†**	**0.849†⇧**	**0.831†**
Left SLFII	**0.906†**	**0.952†⇧**	**0.925†**	**0.986†**	**0.992†⇧**	**0.989†**
Right SLFII	**0.928†**	0.657*⇩	**0.846†**	0.720*	**0.837†⇧**	**0.789†**
Left SLFIII	**0.813†**	**0.804†⇩**	**0.806†**	**0.984†**	**0.866†⇩**	**0.930†**
Right SLFIII	0.544	0.630*⇧	0.605†	**0.961†**	**0.892†⇩**	**0.945†**
Left uncinate	**0.950†**	**0.906†⇩**	**0.937†**	**0.886†**	**0.958†⇧**	**0.909†**
Right uncinate	**0.945†**	**0.888†⇩**	**0.940†**	0.683†	**0.958†⇧**	**0.780†**

Sig 0.050 or below*, Sig 0.005 or below†; (Any ICC values over 0.75 in **bold,** values between 0.5 – 0.7 normal, below 0.5 *red italics*) corpus callosum (CC), rostrum & genu (CC1&2), rostral body (CC3), anterior midbody (CC4), posterior midbody (CC5) isthmus & splenium (CC6&7), frontal aslant tract (FAT), inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF). ⇧ Indicates a trend of increased volume or HMOA with age ⇩indicates a trend of decreased volume or HMOA with age.

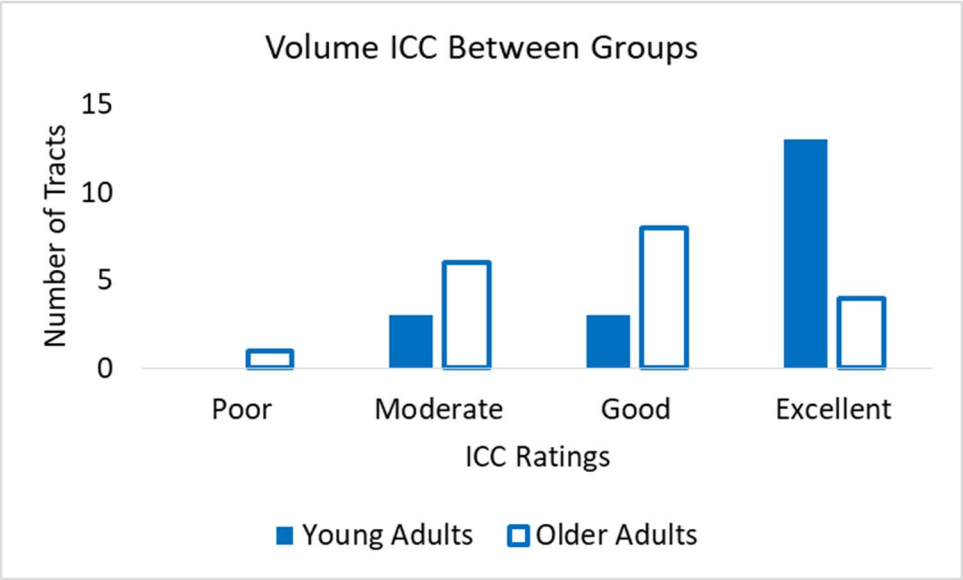


Figure 48 Manual dissection volume reliability categories between groups

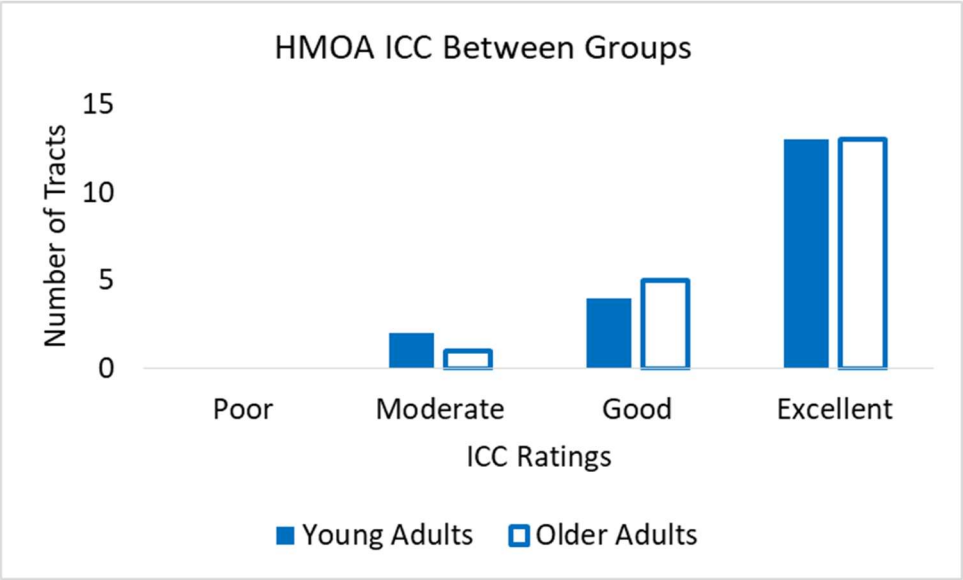


Figure 49 Manual dissection HMOA reliability categories between groups

4.4.4 Comparison between manual and semi-automated methods

Intra-rater ICC's for consistency between manual (round 1) and semi-automated methods are presented in table 14. For tract volume across the whole group all tracts achieved above 0.75 which is deemed good or excellent except for moderate results for the third segment of the corpus callosum (rostral body, 0.694†) the left and right FAT (0.647†, 0.720†) left and right IFOF (0.731†, 0.739†), the left SLFI (0.726†) the right SLFIII (0.662†). For the young adult group all tract volumes achieved ICC of over 0.75 except for the left FAT, bilateral SLFI and the right SLFIII which

achieved moderate reliability scores (between 0.5 – 0.75). For the older adult age group 10 tracts achieved good or excellent reliability. Seven tracts achieved moderate reliability, the bilateral cingulum (0.706*, 0.665*), the left FAT (0.710*), bilateral IFOF (0.539*, 0.508*), right SLFII (0.641*) and the right SLFIII (0.625*). The third segment of the corpus callosum (rostral body, 0.439), the right FAT (0.484), were observed to have very poor reliability.

For HMOA across the whole group all tracts except the right IFOF achieved over 0.75 ICC. For young adults all tracts achieved ICC results of 0.75 or above except for moderate reliability for the right SLFII (0.701*) and right uncinate (0.706*) and very poor reliability for the right IFOF (-0.162). All tracts in the older adult age group achieved < 0.75 ICC except for the left SLFI (0.742*).

Table 14 Manual (Round 1) and semi-automated dissection method ICC (two way mixed, 95% CI, consistency model) results

Tract / Segment	**Volume**			**HMOA**		
	Young adults	Older Adults	Whole Group	Young adults	Older Adults	Whole Group
Left cingulum	**0.847†**	0.706*⇩	**0.782†**	**0.868†**	**0.875†⇧**	**0.881†**
Right cingulum	**0.879†**	0.665*⇩	**0.795†**	**0.913†**	**0.881†⇩**	**0.911†**
CC 1 & 2 combined	**0.933†**	**0.921†⇩**	**0.916†**	**0.928†**	**0.971†⇧**	**0.963†**
CC3 rostral body	**0.938†**	*0.439⇩*	0.694†	**0.956†**	**0.961†⇧**	**0.959†**
CC4 anterior midbody	**0.868†**	**0.888†⇧**	**0.846†**	**0.915†**	**0.861†⇩**	**0.889†**
CC5 posterior midbody	**0.887†**	**0.857†⇩**	**0.874†**	**0.938†**	**0.807†⇩**	**0.885†**
CC6 & 7 combined	**0.931†**	**0.858†⇩**	**0.858†**	**0.985†**	**0.985†**	**0.983†**
Left FAT	0.577*	0.710*⇧	0.647†	**0.987†**	**0.909†⇩**	**0.942†**
Right FAT	**0.974†**	*0.484⇩*	0.720†	**0.975†**	**0.924†⇩**	**0.943†**
Left IFOF	**0.832†**	0.539⇩	0.731†	**0.950†**	**0.949†⇩**	**0.949†**
Right IFOF	**0.858†**	0.508⇩	0.739†	*-0.162*	**0.833†⇧**	0.604†
Left SLFI	0.738*	**0.774†⇧**	0.726†	**0.814†**	0.742*⇩	**0.785†**
Right SLFI	0.708*	**0.873†⇧**	**0.758†**	**0.799†**	**0.859†⇧**	**0.826†**
Left SLFII	**0.900†**	**0.954†⇧**	**0.921†**	**0.986†**	**0.991†⇧**	**0.988†**
Right SLFII	**0.931†**	0.641*⇩	**0.839†**	0.701*	**0.882†⇧**	**0.808†**
Left SLFIII	**0.795†**	**0.789†⇩**	**0.800†**	**0.983†**	**0.976†⇩**	**0.985†**
Right SLFIII	0.645*	0.625*⇩	0.662†	**0.965†**	**0.897†⇧**	**0.948†**
Left uncinate	**0.859†**	**0.811†⇩**	**0.842†**	**0.874†**	**0.939†⇧**	**0.897†**
Right uncinate	**0.932†**	**0.854†⇩**	**0.910†**	0.706*	**0.879†⇧**	**0.756†**

Sig 0.05 or below*, Sig 0.005 or below†; (Any ICC values over 0.75 in **bold** and values below 0.5 in *red italics*) ⇧ indicates a trend of increased volume or HMOA reliability with age ⇩indicates a trend of decreased volume or HMOA reliability with age.

4.4.5 Exploring agreement and bias between methods (Bland-Altman plots)

For volume measurements across the whole group three of the 14 association tracts were observed to have good agreement between manual and automated methods. These were the right FAT, the left IFOF and right SLFIII. All other tracts demonstrated significant differences between means. Megatrack produced consistently higher volume measurements for the left cingulum left FAT, right IFOF, left SLFI, left SLFIII and bilateral uncinate compared to manual dissection methods. It produced consistently lower measurements for the right cingulum, right SLFI, bilateral SLFII and right SLFIII compared to manual dissection methods. Across the association tracts the right FAT, left SLFI and bilateral uncinate had the smallest, the bilateral cingulate, left FAT, left IFOF, left SLFI and bilateral SLFII had intermediate and the right IFOF and right SLFI and right SLFIII had the largest limits of agreement.

For volume measurements of the segments of the corpus callosum two of five were observed to have good agreement in between methods. These were the combined anterior segments 1 & 2 (Rostrum & Genu combined) and the combined posterior segments 6 & 7 (Isthmus and Splenium). Megatrack produced consistently higher measurements for the fourth and fifth segments and consistently lower measurements for the third segment compared to manual dissection methods. Across these segments the most anterior combined segments 1 & 2 (rostrum and genu), segments 4 (anterior midbody) and 5 (posterior midbody) had intermediate limits of agreement and the 3rd (rostral body) and posterior 6 & 7 (isthmus and splenium) had the largest limits of agreement.

For HMOA measurements across the whole group 10 of the 14 association tracts were observed to have good agreement between manual and automated methods. Those that did not were the bilateral cingulum, right SLFI and right SLFII. Megatrack produced consistently higher measurements for the bilateral cingulum and right SLFI compared to manual dissection methods. Megatrack produced consistently lower measurements for the right SLFII compared to manual dissection methods. Across the whole group the left and right FAT, left SLFI and left SLFIII had the smallest, the left and right cingulum, left IFOF, right SLFI and right SLFIII had intermediate and the right IFOF, bilateral SLFIII and bilateral uncinate had the largest limits of agreement.

The left and right IFOF were observed to have potentially non-uniform variability between measurement errors.

For the HMOA measurements of the segments of the corpus callosum 2 of 5 were observed to have good agreement between methods. These were the anterior midbody and posterior midbody. Megatrack produced consistently higher measurements for the second (rostral body) and combined posterior (isthmus and splenium) segments and consistently lower measurements for the combine anterior (rostrum and genu) segments compared to manual dissection methods. Across the group, the combined anterior, third and combined posterior segments had intermediate and the fourth and fifth (anterior and posterior midbody) had largest limits of agreement.

4.5 Discussion

4.5.1 Reliability of manual dissection method

Overall, after merging segments 1&2 and 6&7 of the corpus callosum there was good or excellent reliability of the manual dissection protocols when measuring tract volume across the full participant group for 16 of the 19 tracts/segments. Only the third (rostal body) segment of the corpus callosum was observed to have only moderate reliability. Young adults demonstrated excellent reliability for this segment, but there was a very poor, non-significant result in the older adult age group (ICC -0.104).

For HMOA measurements ICC values were good or excellent for all 19 tracts/segments across the whole group.

Compared to ICC results in the literature reliability of measurements for the cingulum volume are comparable or better and for HMOA they are comparable. The anterior corpus callosum volumes are lower than those published by (Danielian et al., 2010) but reasonably similar to the literature for HMOA. IFOF volume and HMOA ICC values were better than the literature. The uncinate volume and HMOA values were comparable.

There were no studies reporting on ICC measurements for manual dissection protocols of the SLF system and FAT pathways to compare against. However, volume and HMOA measurements for the FAT and SLF fell within the range for other association tracts listed in the literature.

4.5.2 Comparing manual and semi-automated dissection methods

ICC consistency results overall show good reliability between volume measurements made by Megatrack compared to the manual approach, with the exceptions of the third (rostral) corpus callosum segment and the right FAT. As with the manual method, Megatrack proves more reliable when measuring HMOA, indeed for most tracts it achieved excellent scores apart from the right IFOF in the young adult group. Megatrack also reveals similar trends in terms of differences between young and older adults to manual dissection methods. Greatest variability in volume measurements, as illustrated through the Bland Altman plots are found in the right hemisphere, particularly with the right IFOF right SLFI and right SLFIII Greatest variability in HMOA measurements are found in the right IFOF, bilateral SLFIII and bilateral uncinate.

The systematic bias between methods observed for many tracts does not seem to follow a particular pattern, it is tract specific. That is, there is no general trend that shows that Megatrack always produces measurements larger or smaller than the manual method. One possible reason for this could be due to the modified dissection protocols used on the Megatrack dataset. Decisions during the tract dissection for the Megatrack dataset occur once and are applied to the entire group. Therefore, a more generous or more conservative choice of artefact removal is applied consistently across the whole group. Whilst this reduces some variability compared to manual dissection methods, it also propagates potential errors across the whole group. Such bias could cause challenges for subsequent analysis.

Perhaps for future research these initial dissection protocols could be reviewed, amended and re-tested using an iterative process until these inconsistencies are reduced further. Whilst a time-consuming process, this approach is considered best practice in many software industries and would benefit future use of Megatrack. Megatrack appears to be a powerful tool for neuroimaging, but it is very new in terms of development and currently has limitations in its application. However, with diligent testing, it could become an excellent system that could be applied in both research and clinical settings.

4.5.3 Reasons for variability

Variability in measurements can have several different sources. One is the level of heterogeneity within the population itself. A good example of this is the SLF system which demonstrates considerable variability in the positioning of the three tracts in each hemisphere in relation to one another. On a more general note, whilst using the same method, it is clear that reliability is lower for volume measurements compared to HMOA across all tracts in the sample. This could be due to a less heterogeneity across the population in HMOA values.

A second source of variability is measurement error included within the methods themselves. Does the method being assessed accurately reflect the true population? For the manual dissection method, the clarity and accuracy of the directions in the protocol are clearly instrumental. It could be for some tracts that alternative references to anatomical landmarks, or alternative rules in terms of ANDROI and NOTROI placement may produce better reliability overall.

For the semi-automated method there are several differences that may introduce additional variability. The consolidated Megatrack dataset is vast and contains concentrated track details across the entire sample. In this case, dissections were conducted on a merged dataset of 21 separate individuals. This means that there may be a much greater number and variety of artefacts spread across the larger data set to eliminate in one go. However due to the density of the image, not all these artefacts may have been visible to remove. In addition, to merge and extract individual data sets, Megatrack registers and transforms native images to align with an MNI template. These transformations may also introduce another element of change or variability compared to manual dissection.

Thirdly variation can be due to operator bias. Does the operator have enough training, experience and knowledge to use the method correctly? Does the operator have sufficient discipline to faithfully apply the protocol across all tracts in the data set when conducting the dissections? Or is the method so robust a novice could use it without concern for introducing errors. For both the methods explored in this chapter, a certain level of anatomical expertise and experience in tractography is required to be able to identify anatomical landmarks to position regions of interest, and to also spot potential artefacts with crossing fibres systems.

4.5.4 Newly described pathways

The SLF is a relatively recently described fronto-parietal system in terms of DTI tractography (de Schotten, Dell'Acqua, et al., 2011b). During the manual dissection work, some ambiguity was observed in the separation of SLFII from either SLFI or SLFIII. In some instances, the SLFII seemed to be more proximal to the SLFI tract, and in other cases, the SLFII was more proximal to the SLFIII tract. In others, it could not be delineated at all. (see Appendix F for qualitative descriptions). It may be that the protocols were not detailed enough or did not use the most appropriate anatomical landmarks to accurately capture the anatomy of each SLF system for each subject. Despite this, HMOA reliability remained good overall.

The transfer of the manual protocol to the automated one would have suffered additional ambiguity in terms of assessing the split between SLFII and its neighbouring tracts using frontal termination points. In the combined Megatrack tract which was exceptionally thick with streamlines from 21 different subjects, the subtle differences between these termination points would not have been as clearly visible as with a single subject.

The frontal aslant tract (FAT) is another relatively newly described tract in DTI tractography. Perhaps because it is less complex than the SLF system and requires less NOTROIs to be positioned, the manual dissection protocol demonstrated good reliability in the right fat volume measurements and excellent reliability for left volume and bilateral HMOA measurements for the whole group. However, there was a decreased reliability or translation of these protocols using the semi-automated methods for the right FAT in the older adult age group.

4.5.5 Differences between young and older adult age groups.

There were no significant differences between young and older adults in terms of mean volume across all tracts. HMOA did significantly decrease in the bilateral SLFIII and the anterior two segments of the corpus callosum (rostrum and genu).

When using manual dissection protocols, a general trend of decreased reliability in volume measurements with age was noticeable for 13 of the 19 tracts/segments (see table 14). Counter intuitively a trend of slightly more than half the tracts/segments (11 of the 19) *increased* in HMOA with age, although the differences were slight.

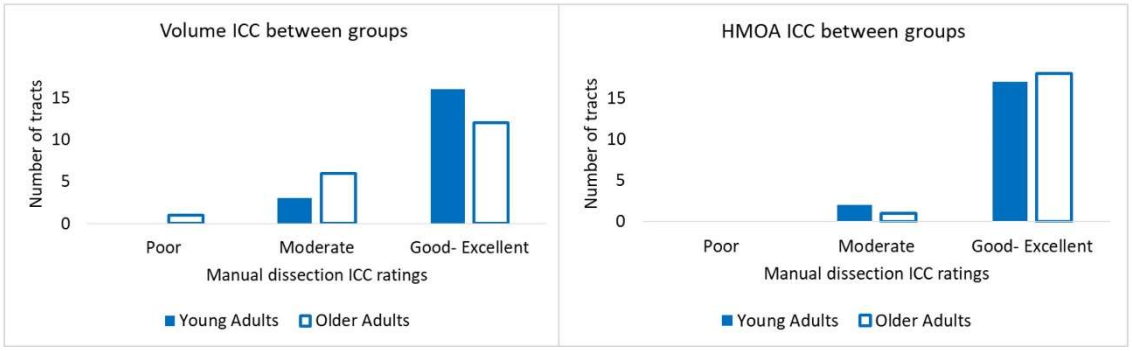


Figure 50 Distribution of tract protocol reliability between age groups for manual method

When comparing manual dissection with semi-automated method the trend of a reduction in volume reliability with age was replicated in 14 of the 19 tracts/segments. The smaller difference between groups and broader spread of increase (11), decrease (6) and no change (2) in measurements of HMOA was also similar to the manual dissection method.

Overall, measurement of HMOA values are reliable for most tracts for young and older adults. However, measurement of volumes for both methods becomes slightly less reliable for older adults. One possible reason could be due to a higher number of artefacts in older adult tracts, although this is speculative and would need to be described and quantified properly.

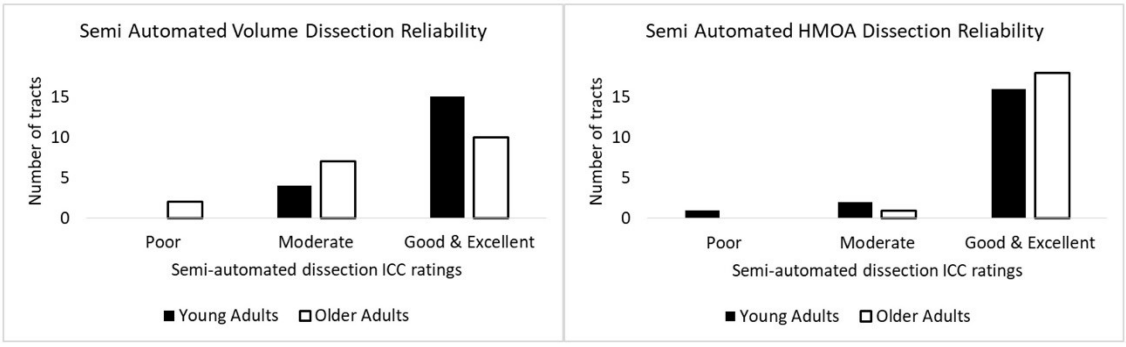


Figure 51 Distribution of tract protocol reliability between age groups for semi-automated method

4.5.6 Limitations of the study

It should be noted that analysis within this chapter has been conducted on a reasonably small data set. Additionally, the semi-automated dissection software is relatively new in its stages of development. It is recommended that more testing of this software be conducted on larger

datasets to provide additional assessments of its reliability. Finally, no comparison between operators has been included in this study for either manual or semi-automated methods. A view of how robust the dissection protocols are when applied by other operators of equal experience and knowledge would provide useful data to further ascertain the full capabilities and limitations of these methods.

4.5.7 Summary and next steps

While HMOA reliability is generally good, the third segment of the corpus callosum, the right FAT and right IFOF demonstrated poor volume or HMOA reliability scores in at least one of the age groups and were therefore removed from further analysis.

Moving forward, it is recommended that the issues with the reliable dissection of these tracts be investigated further. It may be that there are some methodological issues that can be resolved in before using this particular approach for examination of this tract in future. For example, visual inspection and comparison of the automated dissections compared to the manual ones would be essential (as previously mentioned this facility was unavailable at the time). This would enable any issues obvious with the automated dissection protocol to be identified. It could alternatively be that there are discrepancies related to the registration of native images (of individual brains) to template images during the process of aggregating the dataset into a single 'Megatrack' and again when the Megatrack dissections metrics are subsequently separated out. Considering that there does not seem to be the same issue across all tracts, this suggested problem may only become visible in certain tracts due to specific and local idiosyncrasies of the template brain that fall within the path of these specific tracts. This is unlikely, however.

Alternatively, there may be an issue in the quality assurance process of the data and certain images that should have been removed were not. Possibly noise from some images while considered 'acceptable' for manual dissection methods are not for semi-automated methods. A different threshold required. These are just a few suggestions that would need careful validation by the technical teams involved in the development of the software. The only way to identify the cause of these issues is to systematically test each stage of the process until anomalous results are isolated and the cause identified. I do not consider these issues as insurmountable. Regarding any technical issues, in the web development world rigorous testing is required of all new software

code at many different points in the process of development. It is a given that there will be issues that need to be addressed in order to make sure the software is robust and as accurate as possible and can perform under expected load. Building new software is a skill that recruits expertise to be applied in creating new systems that always include an element of the unknown. It is expected that when delving into the unknown arena initial solutions may need to be adjusted (just as in the cognitive process of problem solving, regular feedback and flexibility is required) in order to keep the plan on track towards the overall goal. The same principal applies to any processes involved in quality checking, pre-processing and tract delineation. Megatrack is an excellent and powerful tool that it has been demonstrated works particularly well for many different tracts. The fact that there some anatomical regions that prove more problematic than others simply highlights the need for further investigation.

It is also recommended that reliability analysis of the SLF system is expanded and incorporates a quantitative approach to assessing the frequency of overlap between SLFII to SLFI and SLFIII. This would be a time consuming but reasonably feasible study as the data is already available and the protocols ready for updating. While at the time of preparing the protocols, visual inspection was carried out for every tract in the manual dissection reliability work, as already mentioned it was not possible to do the same with the semi-automated tracts. It may be also that following visual inspection there may still be issues that require more detailed quantification. In this case use of software such as DICE to examine positioning of ROIs or overlap of tracts may give greater accuracy and inform improvement and reliability of the dissection protocol. Alternatively, it may be found that the level of inter-individual variance of SLF system anatomy warrants a different approach entirely (e.g. merging of tracts per hemisphere).

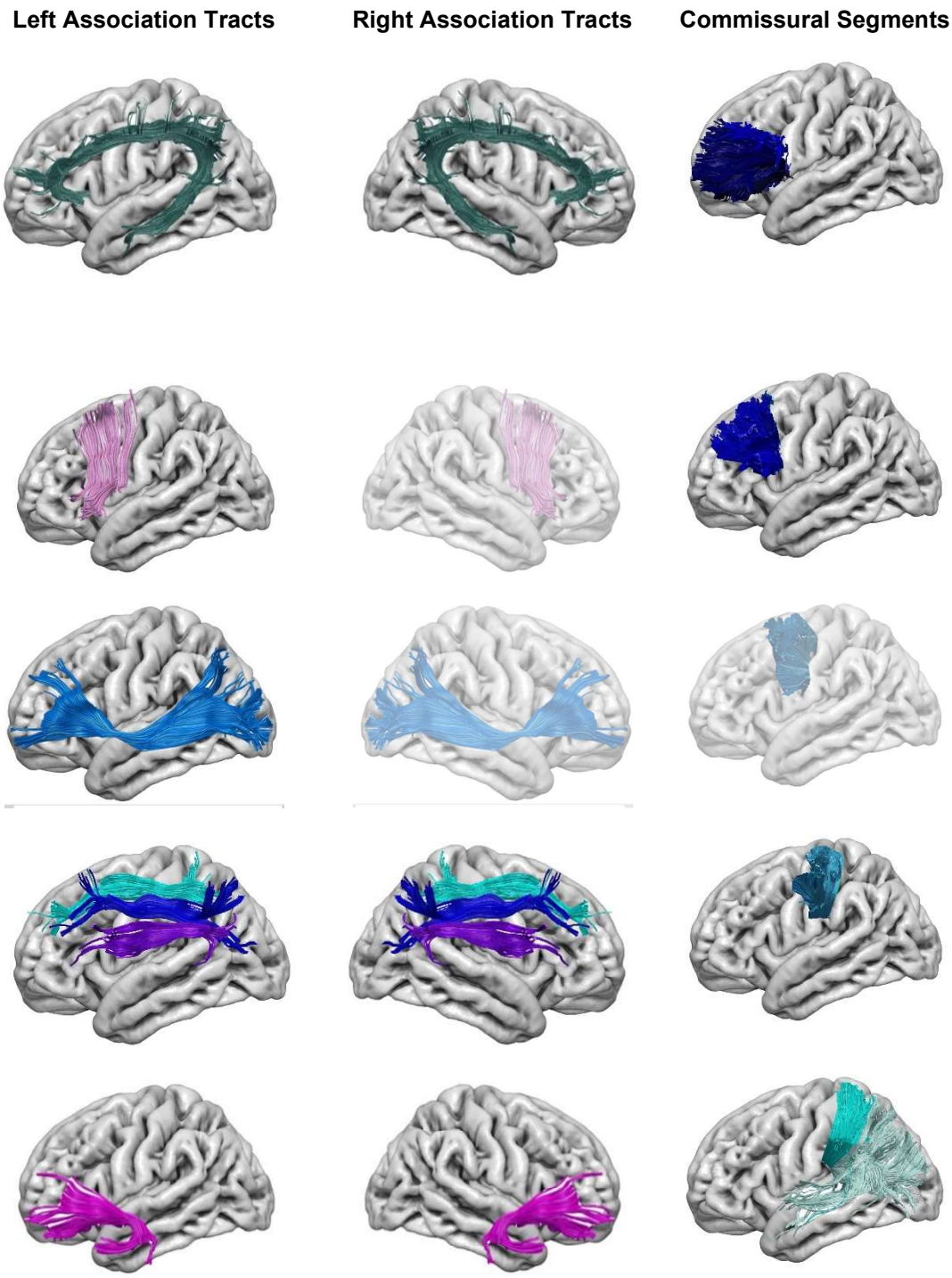


Figure 52 Good to excellent reliability of HMOA measurements between methods [reliable tracts in bold]

Table 15 Mean Volumes and HMOA of all tracts and segments

Tract Segment	***Mean Volume (Man r1)***			***Mean HMOA (Man r1)***		
	Young adults (SD)	Older Adults (SD)	Whole Group (SD)	Young adults (SD)	Older Adults (SD)	Whole Group
Left cingulum	27.36 (6.10)	29.34 (6.10)	28.35 (5.29)	0.019 (0.002)	0.021 (0.002)	0.0200 (0.002)
Right cingulum	24.91 (5.90)	26.82 (5.90)	25.87 (4.97)	0.016 (0.002)	0.019 (0.002)	0.0171 (0.002)
CC1&2	58.11 (11.53)	57.97 (10.52)	58.04 (10.71)	0.026 (0.001)	0.024 (0.003)	0.025 (0.003)
CC3	50.20 (13.88)	45.34 (13.88)	47.77 (11.50)	0.021 (0.002)	0.020 (0.003)	0.021 (0.003)
CC4	45.20 (11.20)	44.48 (11.20)	44.84 (9.22)	0.024 (0.003)	0.023 (0.003)	0.024 (0.003)
CC5	42.18 (11.83)	43.63 (11.83)	42.91 (10.61)	0.028 (0.004)	0.027 (0.002)	0.027 (0.003)
CC6&7	119.29 (21.69)	119.24 (21.69)	119.26 (21.23)	0.029 (0.003)*	0.029 (0.004)*	0.029 (0.004)
Left FAT	11.23 (4.11)	11.11 (4.11)	11.17 (4.56)	0.017 (0.001)	0.016 (0.002)	0.016 (0.001)
Right FAT	9.38 (2.54)	9.24 (2.54)	9.31 (2.17)	0.016 (0.001)	0.016 (0.002)	0.016 (0.001)
Left IFOF	31.39 (7.79)	29.83 (7.79)	30.61 (6.37)	0.022 (0.002)	0.023 (0.004)	0.02 (0.003)
Right IFOF	28.71 (9.34)	28.62 (9.34)	28.66 (8.14)	0.023 (0.002)	0.023 (0.003)	0.02 (0.003)
Left SLFI	16.74 (7.43)	20.41 (7.09)	17.25 (6.34)	0.011 (0.001)	0.010 (0.001)	0.010 (0.001)
Right SLFI	19.89 (7.09)	17.76 (7.43)	20.15 (7.18)	0.011 (0.001)	0.010 (0.002)	0.011 (0.001)
Left SLFII	9.54 (5.54)	5.46 (5.54)	7.50 (4.91)	0.012 (0.005)	0.010 (0.005)	0.011 (0.005)
Right SLFII	13.93 (5.54)	9.06 (5.54)	11.50 (5.60)	0.017 (0.003)	0.017 (0.004)	0.017 (0.004)
Left SLFIII	10.13 (2.83)*	9.04 (2.83)*	9.59 (2.99)	0.016 (0.002)	0.014 (0.002)	0.015 (0.002)
Right SLFIII	18.41 (5.88)*	14.56 (5.88)*	16.49 (5.29)	0.020 (0.002)	0.018 (0.002)	
Left SLFI-III	36.42 (10.30)*	32.26 (10.30)*	34.34 (9.31)	0.013 (0.001)	0.011 (0.001)	0.012 (0.001)
Right SLFI-III	52.23 (12.99)*	44.04 (12.99)*	48.14 (12.16)	0.016 (0.001)	0.014 (0.000)	0.015 (0.001)
Left uncinate	11.44 (7.01)	11.62 (7.01)	11.62 (3.69)	0.015 (0.003)	0.015 (0.002)	0.015 (0.002)
Right uncinate	10.49 (5.77)	13.74 (5.77)	13.74 (2.87)	0.016 (0.002)	0.016 (0.002)	0.016 (0.002)

Significant difference between young and older adult groups P = < 0.05

Table 16 Differences between means for all tracts/segments used in Bland Altman plots

Tract	Volume			HMOA		
	Diff from Mean	SD	P value	Diff from Mean	SD	P value
CING left	**4.76**	**3.03**	**0.000**	**-0.002**	**0.001**	**0.000**
CING right	**-2.25**	**3.32**	**0.008**	-0.001	0.001	
CC1&2	1.59	4.28	0.133	**-0.000**	**0.001**	**0.019**
CC3 (Rostral Body)	**-14.12**	**9.03**	**0.000**	**0.000**	**0.001**	**0.031**
CC4 (Anterior Midbody)	2.80	4.97	0.029	0.000	0.001	0.227
CC5 (Posterior Midbody)	**5.89**	**4.89**	**0.000**	0.000	0.001	0.921
CC6&7	-1.99	10.41	0.429	**0.000**	**0.001**	**0.030**
FAT Left	**-1.89**	**3.40**	**0.031**	0.000	0.001	0.922
FAT Right	0.85	1.57	0.071	0.000	0.001	0.495
IFOF Left	1.47	4.36	0.171	-0.000	0.001	0.667
IFOF Right	**11.67**	**6.27**	**0.000**	-0.000	0.003	0.941
SLFI Left	**3.68**	**3.91**	**0.001**	0.000	0.001	0.195
SLFI Right	**6.20**	**5.91**	**0.000**	0.001	0.001	0.008
SLFII Left	**-4.96**	**3.91**	**0.000**	-0.001	0.004	0.337
SLFII Right	**-3.84**	**3.36**	**0.000**	-0.001	0.004	0.346
SLFIII Left	**2.20**	**2.62**	**0.002**	-0.000	0.001	0.194
SLFIII Right	-2.07	4.76	0.083	-0.000	0.001	0.082
UNC	0.30	9.90	0.900	**0.001**	**0.001**	**0.000**
UNC Left	**4.07**	**2.77**	**0.000**	0.000	0.001	0.695
uncinate (sphere) Right	**3.55**	**1.92**	**0.000**	0.000	0.001	0.809

Chapter 5 Results

5.1 Ageing, white matter and selective attention

In answer to the research question '*Does microstructure of the cingulum play a mediatory role in the age-related decline in selective attention in healthy adults?'* it was not possible to demonstrate a significant mediation effect of cingulum HMOA on age related change to selective attention. That is, we could not refute the null hypothesis: 'We predict that no relationship between cingulum HMOA and selective attention performance will be observed, and no significant mediation effect will be found to influence the negative relationship between age and selective attention in healthy adults.'

5.1.1 Reliability of tractography protocols

Reliability of both manual and semi-automated dissection protocols was proven acceptable for measures of volume and HMOA for the bilateral cingulum.

5.1.2 Preliminary regression analysis

A significant negative relationship with age was demonstrated with the color-word remapping task measuring selective attention. Age explained 22% of performance decline.

A significant negative relationship between age and left cingulum HMOA was demonstrated. Age explained 13% of HMOA decline for the left cingulum. The right cingulum demonstrated a trend towards age related decline, but this was not significant ($p = 0.063$) so this tract was excluded from subsequent analysis.

5.1.3 Preliminary correlation analysis

No significant correlation was found between selective attention performance and HMOA of the left cingulum. Therefore, no mediation analysis was conducted.

Table 17 Tract HMOA and age and HMOA and selective attention

Tract	HMOA and Age (Regression)	HMOA and selective attention (Correlation)
Left cingulum	0.1296*	0.123
Right cingulum	0.0409	-0.084

*(*p = <0.5)*

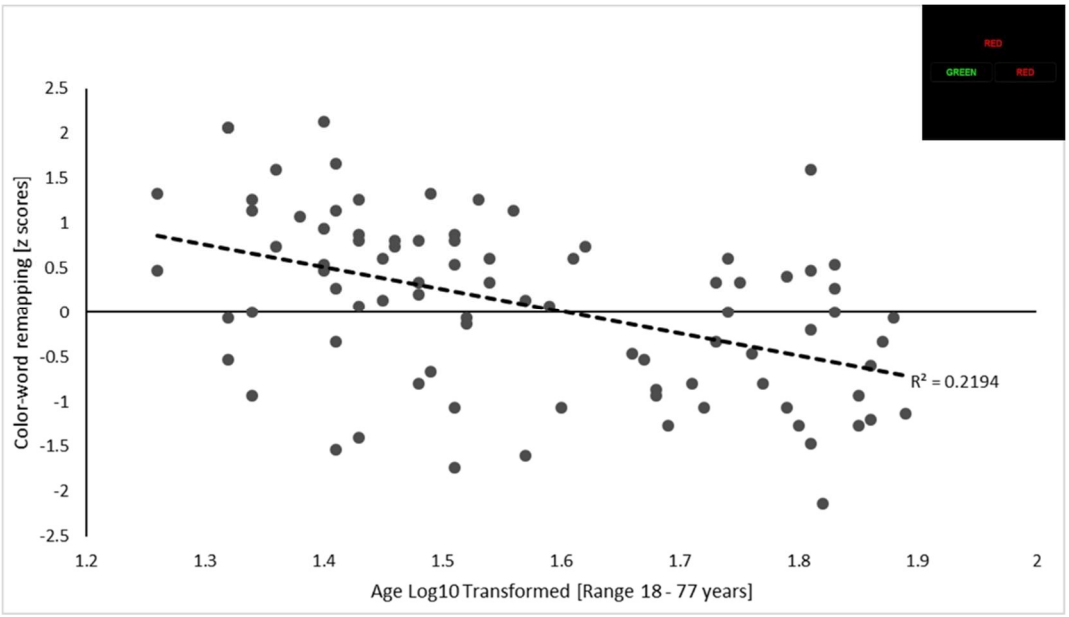


Figure 53 Relationship between age and color-word remapping task performance

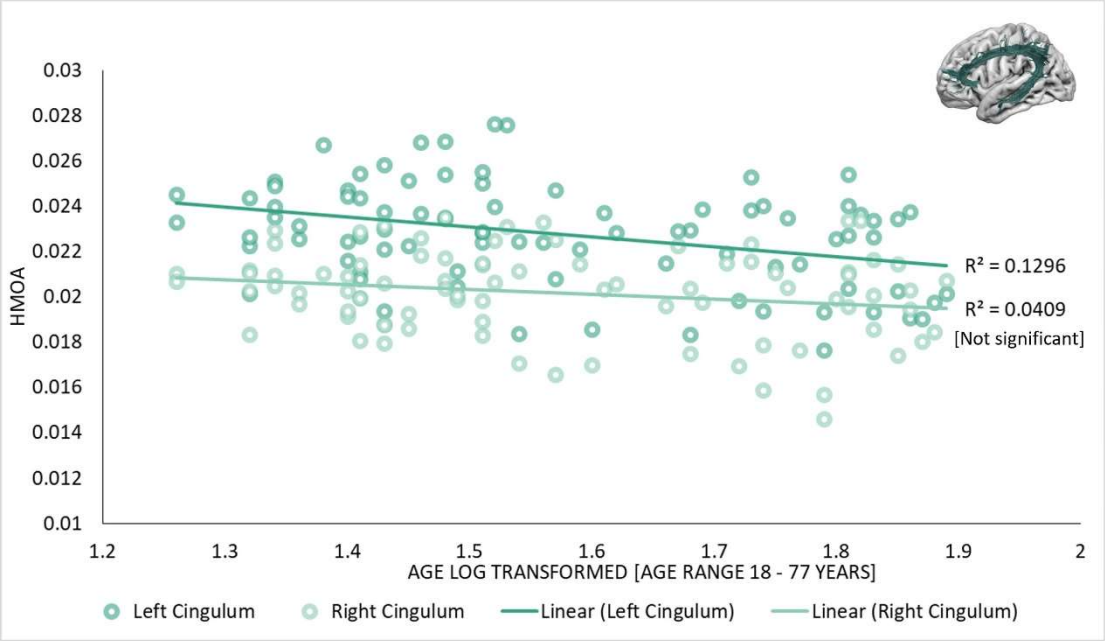


Figure 54 Relationship between age and cingulum HMOA

5.2 Ageing, white matter and spatial working memory

In response to the research question: '*Does microstructure of the cingulum, inferior fronto-occipital fasciculus and superior longitudinal fasciculus system play a mediatory role in the age-related decline in spatial working memory in healthy adults?'* we could not demonstrate a significant mediation effect related to any of the tracts of interest on age associated changes to spatial working memory. That is, we could not refute the null hypothesis: 'We predict that no significant mediation effect will be found regarding microstructure of any of these pathways to influence the negative relationship between age and selective attention in healthy adults.'

5.2.1 Reliability of tractography protocols

Reliability of both manual and semi-automated dissection protocols was proven acceptable for measures of volume and HMOA for the SLF I, SLF II, SLF III, the right SLF I and II. Reliability of measures of volume using the manual dissection protocol for the right SLFIII was low (0.544). It is recommended that any results concerning this tract in subsequent analysis be treated with caution. Measures of volume and HMOA using the semi-automated dissection protocols for the right IFOF were unacceptable in the young adult group and this tract was excluded form subsequent analysis.

5.2.2 Preliminary regression analysis

A significant negative relationship with age was demonstrated with performance on the spatial span task. Age explained 25% of decline in performance.

A significant negative relationship between age and HMOA of the left cingulum, left IFOF, left SLF III and all three segments of the right SLF system was demonstrated. Age explained 13% HMOA decline for the left cingulum 25% for the left IFOF, 8% for the left SLF III, 6% for the right SLFI, 11% for the right SLF II and 16% for the right SLF III. No significant age-related changes to HMOA were observed in the right cingulum, left SLF I or left SLF II. Age related decline of the right SLF I did not survive correction for multiple comparisons and the left SLF III fell on the threshold of significance (9 tracts, = 0.05 / 9 = $p < 0.006$).

5.2.3 Preliminary correlation analysis

After correction for handedness two of the nine tracts revealed a significant correlation with the spatial span task. These were the left cingulum (r = 0.245, p = <0.05) and left IFOF (r = 0.331, p = < 0.005). Correlations between task performance and the left cingulum did not survive multiple comparisons (9 tracts = 0.05 / 9 = p 0.006).

5.2.4 Mediation analysis

The only tract that demonstrated a significant relationship with age and task performance was the left IFOF. When mediation analysis was run, paths a and c were significant, but path b was not. Thus, not all pre-requisites for a causal steps mediation effect were demonstrated. While there were changes (i.e. a slight increase in the coefficient and decrease in significance) between the direct (path c) to the indirect (path c') model, this was very slight (partial). Furthermore, no significant indirect effects were observed.

Table 18 Significance of paths a,b,c & c' when considering age, spatial working memory and left IFOF hmoa

	Coefficient	**SE**	**Significance**
Path a (Age & left IFOF hmoa)	-.0077	.0014	.000
Path b (left IFOF hmoa and spatial working memory performance)	25.5500	32.8087	.4383
Path c (age and spatial working memory performance)	-2.2932	.4349	.0000
Path c' (age and spatial working memory performance controlling for left IFOF hmoa)	-2.0987	.5043	.0001

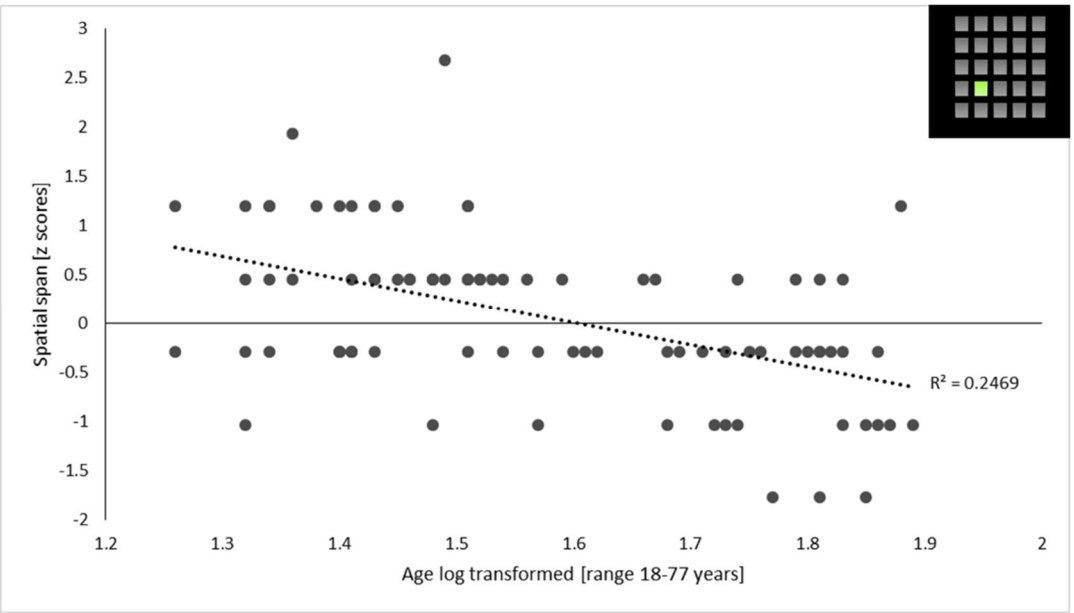


Figure 55 Relationship beween age and spatial span performance

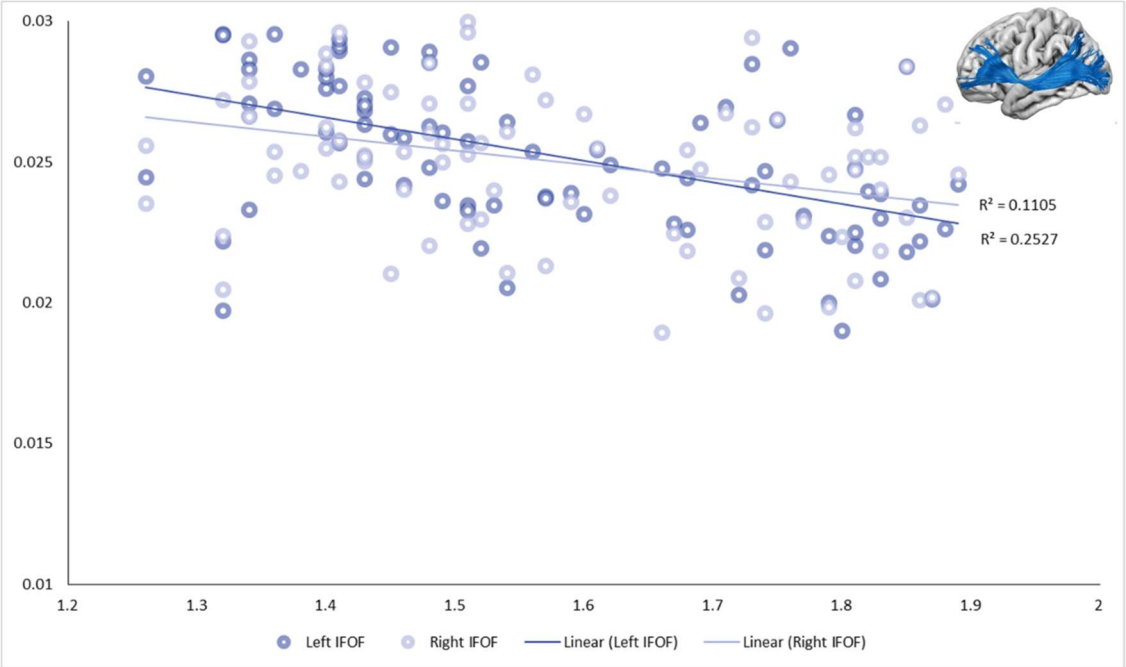


Figure 56 Relationship between age and IFOF HMOA

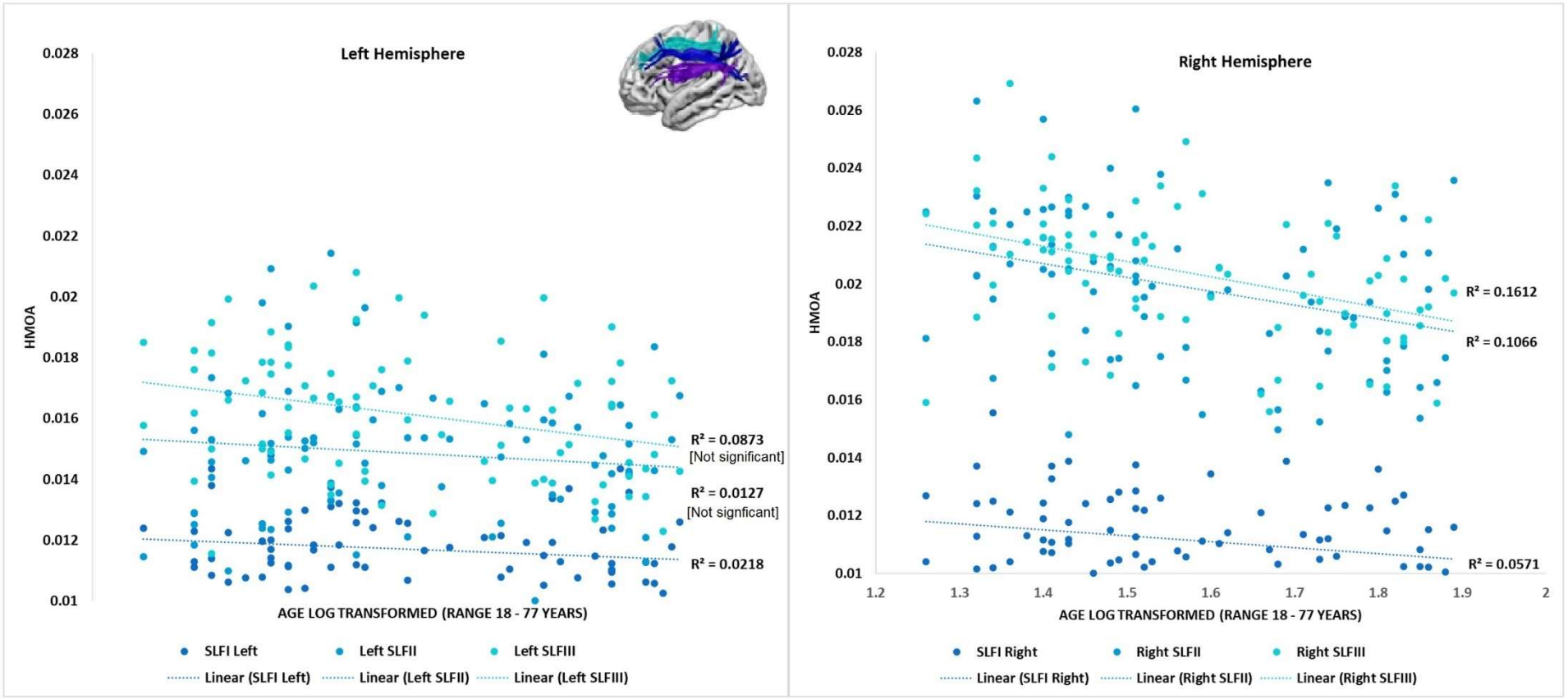


Figure 57 Relationship between age and SLF system HMOA

Table 19 Tract HMOA and age and HMOA and spatial working memory (SWM)

Tract	HMOA and Age (Regression)	HMOA and SWM (Correlation)
Left cingulum	**0.1296***	0.245
Right cingulum	0.0409	0.122
Left IFOF	**0.2527***	**0.331***
Left SLF I	0.0218	0.116
Right SLF I	0.0571	0.108
Left SLF II	0.0127	0.069
Right SLF II	**0.1066***	0.005
Left SLF III	**0.0873***	0.203
Right SLF III	**0.1612***	0.178

*(*p = <.05) HMOA and age and correlation results corrected for multiple comparisons as previously described.*

5.3 Ageing, white matter and planning

In response to the research question: 'D*oes microstructure of the cingulum, inferior fronto occipital fasciculus and superior longitudinal fasciculus system play a mediatory role in the age-related decline in planning in healthy adults?'* we could not demonstrate any significant mediation effects on age related change to planning performance. That is, we could not refute the null hypothesis: 'We predict that despite the indication that a broad network of frontal white matter pathways may be attributed to the function of planning, no relationship between cingulum, IFOF nor SLF system HMOA and planning performance will be observed, and no significant mediation effect will be found from any of these pathways to influence the negative relationship between age and planning ability in healthy adults.'

5.3.1 Reliability of tractography protocols

As previously mentioned, measures of volume and HMOA using the semi-automated dissection protocols for the right IFOF were low and this tract was excluded form subsequent analysis. All other tracts achieved acceptable reliability scores for both manual and semi-automated dissection protocols.

5.3.2 Preliminary regression analysis

A significant negative relationship with age was demonstrated with the spatial planning task. Age explained 20% of performance decline.

All age-related declines in HMOA of the tracts of interest have already been reported in sections 5.1 and 5.2.

5.3.3 Preliminary correlation analysis

After correction for handedness one tract revealed a significant correlation with the spatial planning task. This was the right SLF III ($r = 0.331$, $p = < 0.03$). However, this correlation did not survive correction for multiple comparisons ($0.05 / 9$ tracts = $p < 0.006$).

5.3.4 Mediation analysis

No candidate tracts from those listed in the hypothesis were identified (i.e. no tracts demonstrated significant relationships with age and task performance) thus no mediation analysis was conducted.

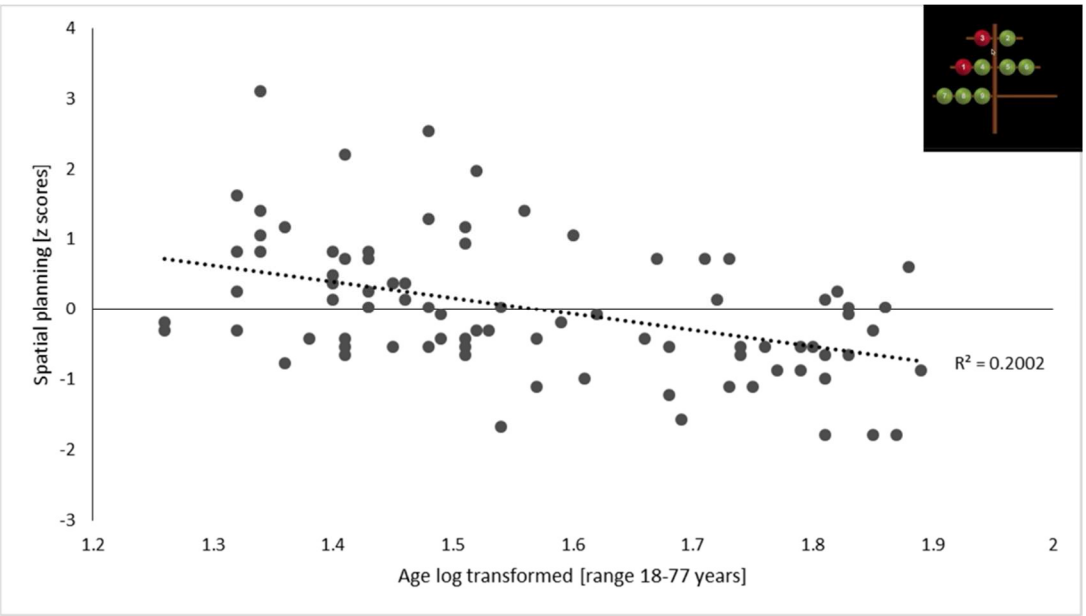


Figure 58 Relationship between age and spatial planning performance

Table 20 Tract HMOA and age and HMOA and spatial planning

Tract	HMOA and Age (Regression)	HMOA & Planning (Correlation)
Left cingulum	**0.1296***	0.123
Right cingulum	0.0409	0.177
Left IFOF	**0.2527***	0.204
Left SLF I	0.0218	0.038
Right SLF I	0.0571	0.023
Left SLF II	0.0127	0.101
Right SLF II	**0.1066***	0.085
Left SLF III	**0.0873***	0.168
Right SLF III	**0.1612***	0.248

*(*p = <.05) HMOA and age and correlation results corrected for multiple comparisons as described in section 3.6*

5.4 Exploratory analysis

5.4.1 Executive function and age

In addition to the three tasks referred to in the research questions above, another three measuring different processes associated with executive function or memory were included in exploratory analysis. These were tests measuring visuospatial attention (feature match), spatial search (self-ordered search) and paired associates learning (paired associates).

All three of these tasks demonstrated a significant negative relationship with age. Age explained 19% of performance decline changes for the feature match task, 11% for the paired associates task and 9% for self-ordered search task.

5.4.2 HMOA and age

In addition to the 10 tracts referred to in the three research questions above, four tracts (bilateral frontal aslant tract and bilateral uncinate) and five segments of the corpus were identified as candidates for inclusion in the exploratory analysis. However, following testing of manual and semi-automated dissection protocols, the right FAT and third segment of the corpus callosum demonstrated unacceptable levels of reliability and were removed from subsequent analysis.

Of the remaining tracts, a significant negative relationship with age was demonstrated with HMOA for three tracts and the anterior segment of the corpus callosum (combined segment incorporating the rostrum and genu). Age explained 6% decline in HMOA for the anterior corpus callosum, 7% for the left FAT, 11% decline in HMOA for the left uncinate and 6% decline in HMOA for the right uncinate. No significant relationship between HMOA and age was demonstrated for the posterior segments of the corpus callosum.

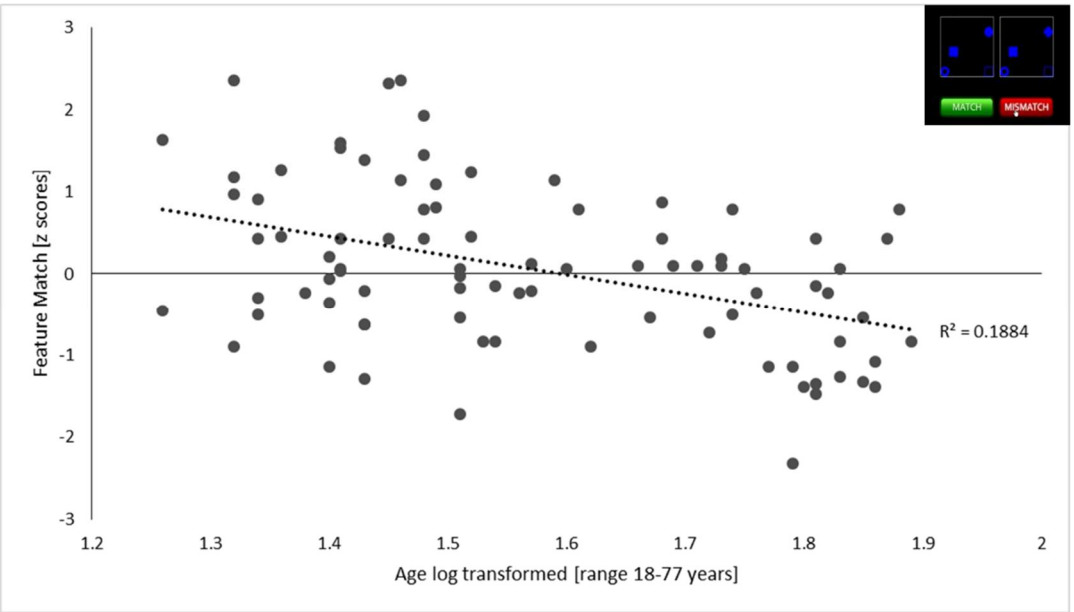


Figure 59 Relationship between age and feature match performance

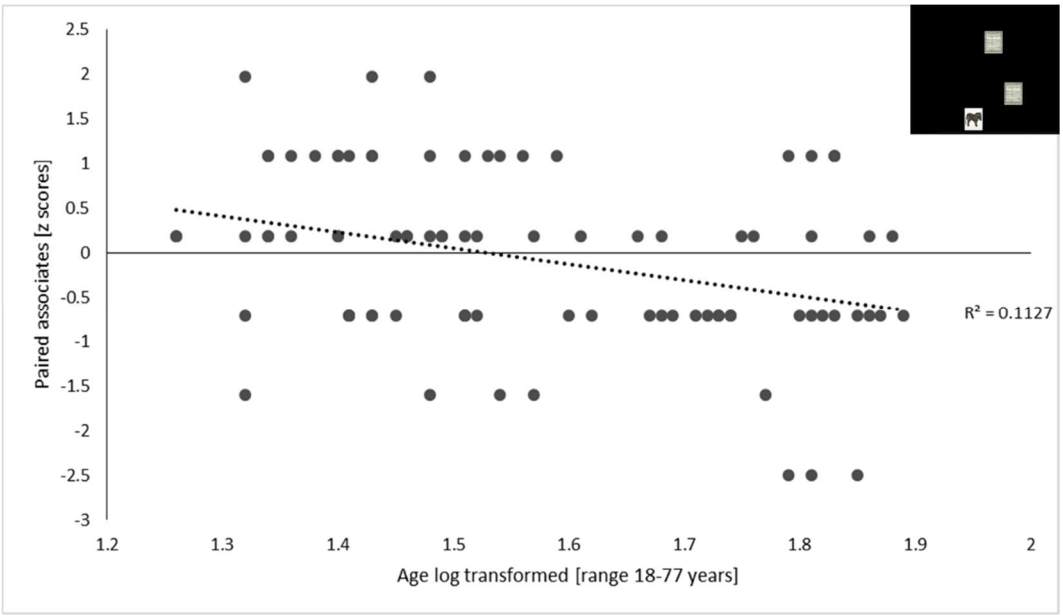


Figure 60 Relationship between age and paired associates performance

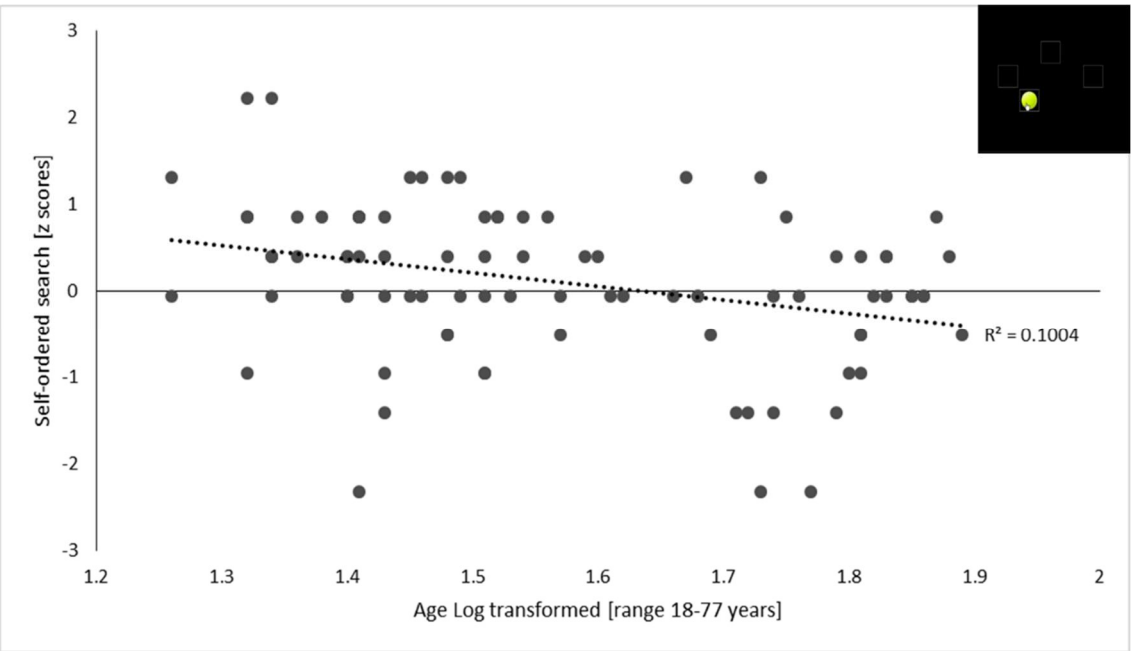


Figure 61 Relationship between age and self-ordered search performance

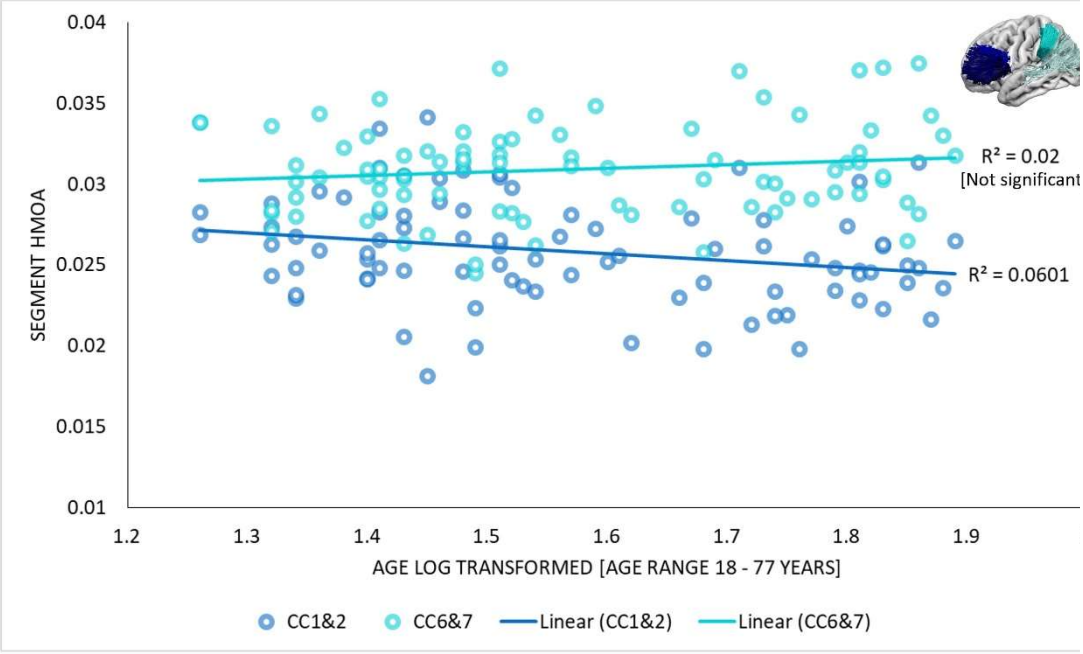


Figure 62 Relationship between age and HMOA of the anterior (combined rostrum and genu) and posterior (combined isthmus and splenium) segment of the corpus callosum

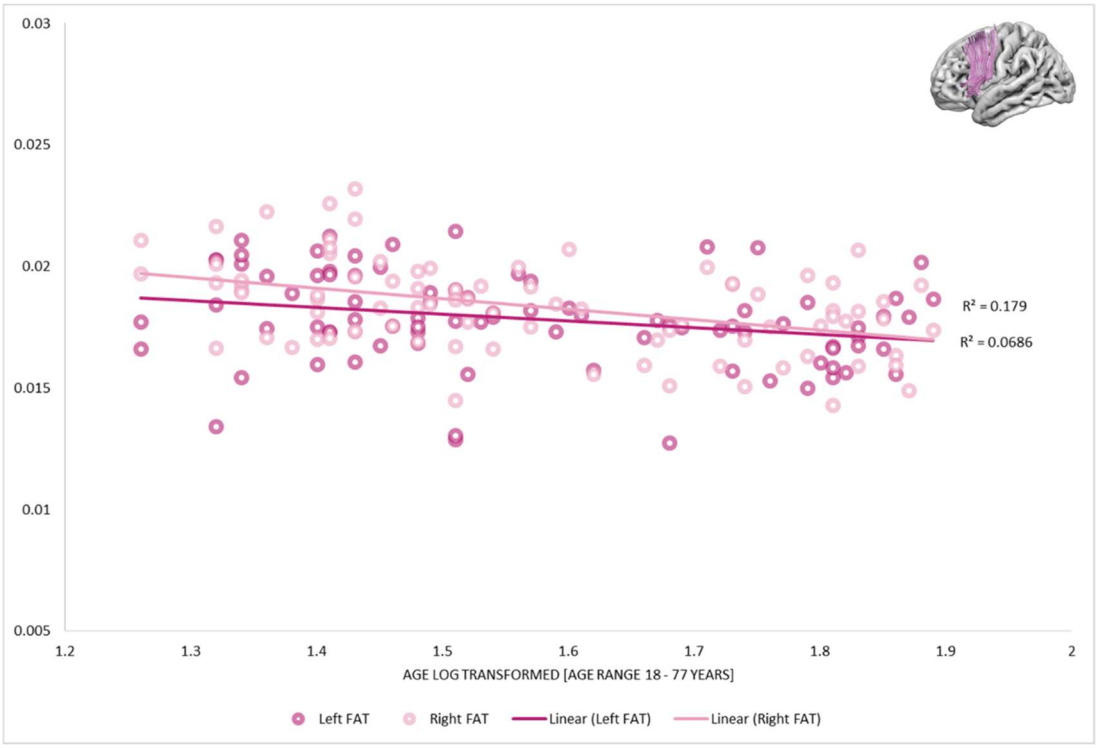


Figure 63 Relationship between age and FAT HMOA

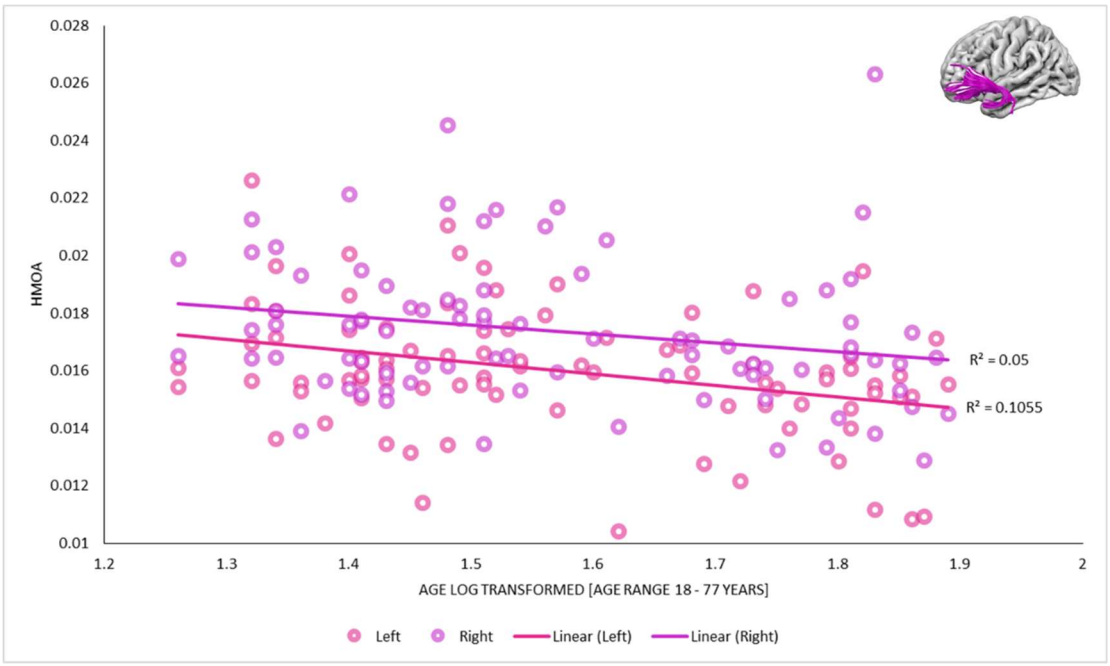


Figure 64 Relationship between age and uncinate HMOA

5.4.3 Correlation between HMOA and executive function

Table 21 shows the correlation analysis between all tracts and behavioural tasks included in both the analysis related to the three discrete research questions and the exploratory analysis.

After correction for handedness one tract revealed a significant correlation with color-word remapping task performance. This was the left IFOF (r = .378, p = 0.001)

Two tracts, the left cingulum (r = .274, p = 0.018) and the left IFOF (r = .345, p = 0.003) demonstrated a significant positive correlation between HMOA and performance for the feature match task.

Seven tracts demonstrated a significant positive correlation between HMOA and paired associate task performance. These were the bilateral cingulum (left r =409, p = 0.000, right r = .391, p = 0.001), the left IFOF (left r = .386, p = 0.001,) the bilateral SLFI (left r = .315, p = 0.006, right r = .246, p = 0.035), right SLFII (r = .276, p = 0.017), and right SLFIII (r = .294 p = < 0.011).

One tract demonstrated a significant correlation with the self-ordered search task performance. This was the left IFOF (r = .254, p = 0.029).

Two tracts demonstrated a positive correlation with the spatial planning task. These were the right SLFIII (r = .248, p = 0.033) and the left uncinate (r = .281, p = 0.015)

Two tracts demonstrated a significant positive correlation between HMOA and performance for the spatial span task. These were the left cingulum (r = .245, p = 0.035) and the left IFOF (r = 0.331, p = < 0.004).

Three tasks were grouped together into an performance index representing the Short Term Memory factor identified by (Hampshire et al., 2012). These tasks were the spatial search, self-ordered search and paired associates. Significant correlations between this group and six of the 19 tract/segments were observed. These tracts were the bilateral cingulum (left r = .334, p =

0.004, right r = .270, p = 0.020), bilateral IFOF (left r = .406, p = 0.000, right r = .241, p = 0.039), left SLFI (r = .241, p = 0.038), and the right SLFIII (r = .254, p = 0.029)

The only task-tract correlations that survived Bonferroni multiple comparisons correction were the significant positive relationship between left cingulum HMOA and paired associate's task performance and the correlation between the left IFOF and performance of the aggregated Short term memory score. (19 tracts x 6 tasks (STM not included) = 114. 0.05 / 114 = 0.00043 or 19 x 7 tasks = 0.05 / 133 = 0.00038).

Table 21 Correlation between HMOA and executive function (controlled for handedness)

Tract HMOA	**Color-word remapping**	**Feature Match**	**Paired Associates**	**Self-Ordered Search**	**Spatial Planning**	**Spatial Span**	**STM Group**
Left cingulum	0.123	**0.274***	**0.409†**	0.144	0.123	0.245	**0.334†**
Right cingulum	-0.084	0.116	**0.391†**	0.135	0.177	0.122	**0.270***
CC1&2 ROS-GEN	(0.048)	0.079	0.112	-0.091	0.099	0.062	0.036
CC3 ROB	-	-	-	-	-	-	-
CC4 ANT	0.006	-0.010	-0.199	-0.213	0.009	-0.065	-0.198
CC5POS	0.147	0.040	-0.027	-0.062	0.006	-0.055	-0.060
CC 6&7ISTSPL	-0.019	0.053	0.055	-0114	-0.025	-0.055	-0.048
Left FAT	0.131	0.150	0.121	0.094	0.179	0.033	0.102
Right FAT	-	-	-	-	-	-	-
Left IFOF	**0.378†**	**0.345†**	**0.386†**	**0.254***	0.204	**0.331***	**0.406†**
Right IFOF	-	-	-	-	-	-	-
Left SLFI	-0.025	0.085	**0.315***	0.148	0.038	0.116	**0.241***
Right SLFI	-0.009	0.168	**0.246***	0.033	0.023	0.108	0.162
Left SLFII	-0.103	-0.068	0.139	0.015	0.101	0.069	0.094
Right SLFII	0.105	-0.218	**0.276***	-0.019	0.085	0.005	0.109
Left SLFIII	0.016	0.154	0.221	-0.106	0.168	0.203	0.136
Right SLFIII	0.215	-0.007	**0.294***	0.137	0.248	0.178	**0.254***
Left uncinate	0.136	0.120	0.173	0.064	**0.281***	0.223	0.194
Right uncinate	0.109	0.156	0.187	0.080	0.147	0.050	0.132

(*p = <.05, †= < 0.005). Results in shaded sections are previously reported and where relevant have been corrected for multiple comparisons

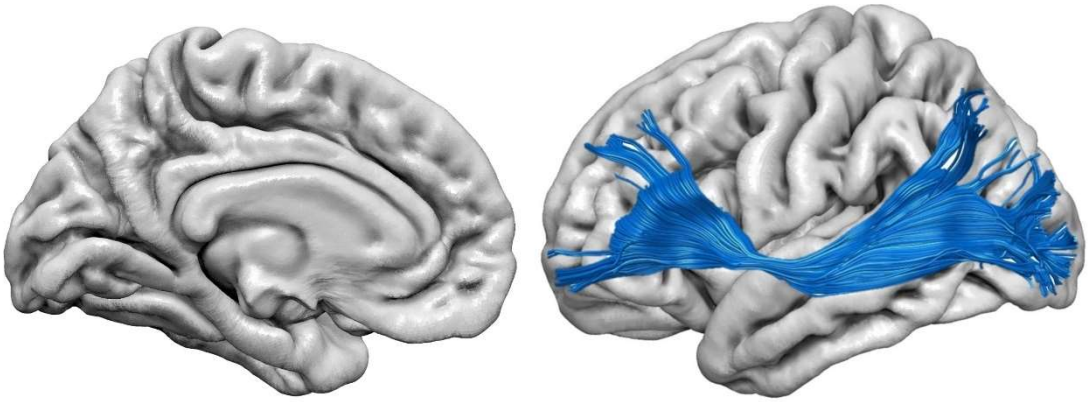


Figure 65 Correlation between left IFOF HMOA and colour-word remapping performance

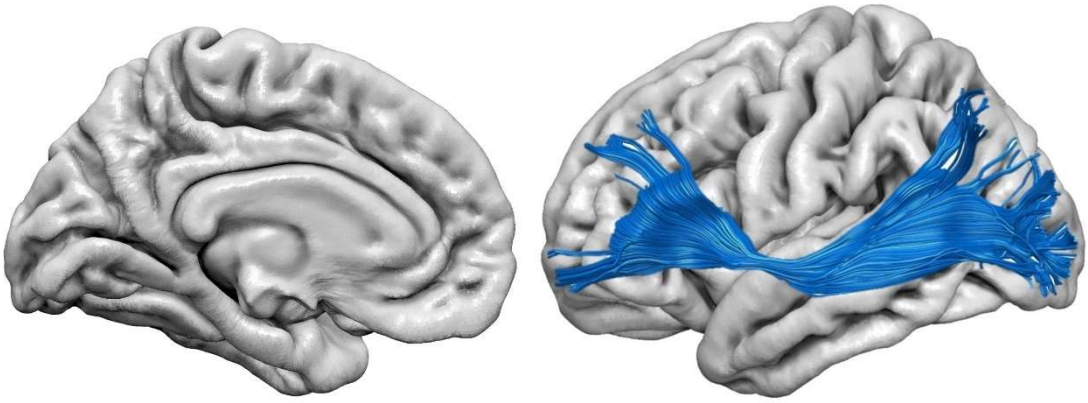


Figure 66 Correlation between left IFOF HMOA and spatial span performance

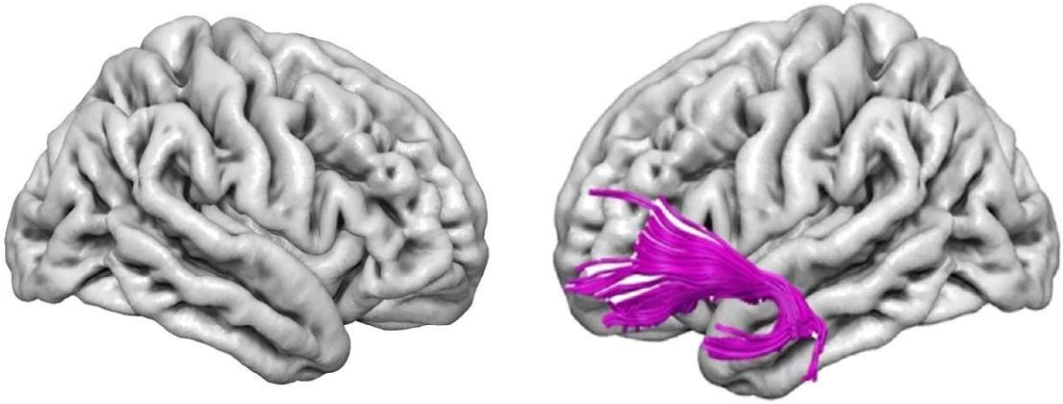


Figure 67 Correlation between left uncinate HMOA and spatial planning performance

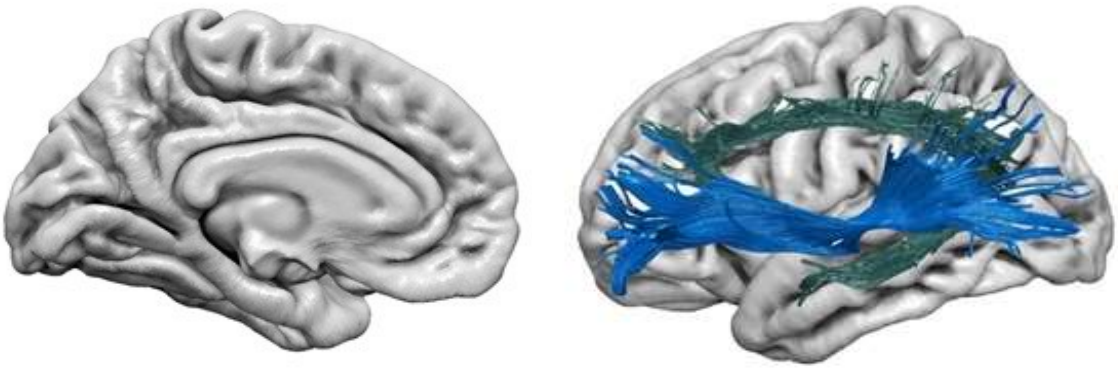


Figure 68 Correlation between left cingulum and IFOF HMOA and feature match performance

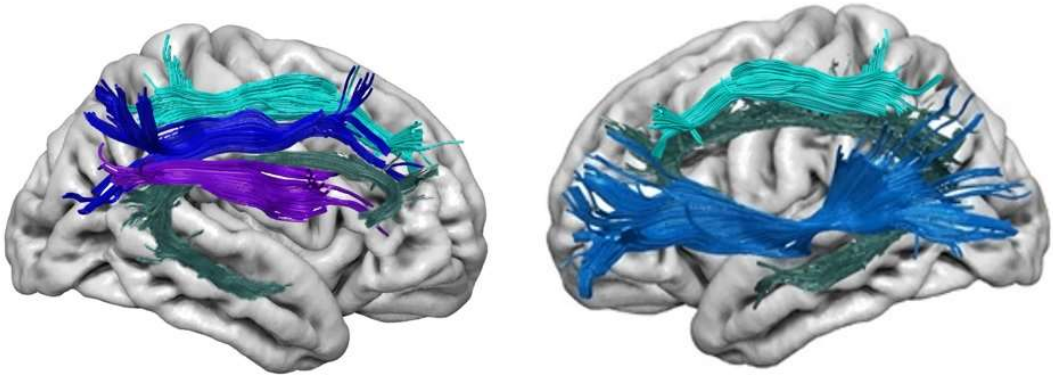


Figure 69 Correlation between bilateral cingulum, IFOF and SLFI, right SLFII & III HMOA and paired associates' performance

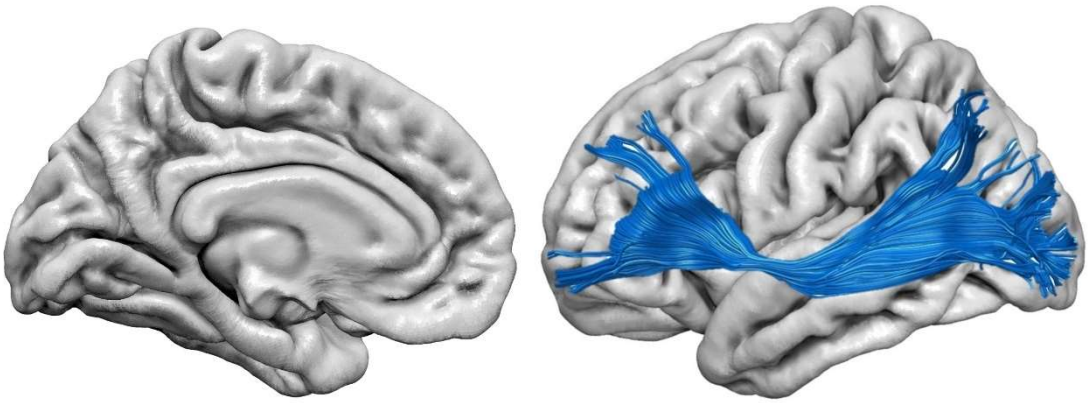


Figure 70 Correlation between left IFOF HMOA and Self-ordered search performance

5.4.4 Mediation

Although one candidate tract (the left IFOF) was identified for mediation analysis for the color-word remapping task no significant mediation or indirect effects of age on performance were observed.

For the spatial span task, no additional tracts were identified as candidate tracts for mediation analysis.

For the feature match task the left cingulum and left IFOF were identified as candidate tracts for mediation analysis but no significant indirect effects of age on performance were observed. Likewise, for the self-ordered search task, while the left IFOF was identified as a candidate for mediation analysis, no significant indirect effects of age on performance were observed.

For the spatial planning task, the left uncinate was identified as a candidate tract for mediation analysis. Results showed that as per the logic of Baron and Kenny, there were significant relationships for paths a, b & c , and when comparing path c and c', the coefficient and significance of the relationship between age and spatial planning performance decreased to some degree (see table 22) when including the mediator in the model. However, the mediation effect was only partial. When considering the indirect effect as calculated using a boostrap confidence intervals method, a significant indirect effect of age on spatial planning performance through left uncinate HMOA was observed, b = -0.355, BCa [-0.965, -0.035]. This was a reasonably small to medium effect: r^2 = 0.0715, SE 0.0362, BCa [-.0171, .1657].

Table 22 Significance of paths a,b,c & c' when considering age, spatial planning and left uncinate hmoa

	Coefficient	SE	Significance
Path a (Age & left uncinate hmoa)	-.0040	.0013	.0021
Path b (left uncinate hmoa and spatial planning performance)	88.1691	43.031	.0436
Path c (age and spatial planning performance)	-2.3463	.5112	.0000
Path c' (age and spatial planning performance controlling for left uncinate hmoa)	-1.9910	.5308	.0003

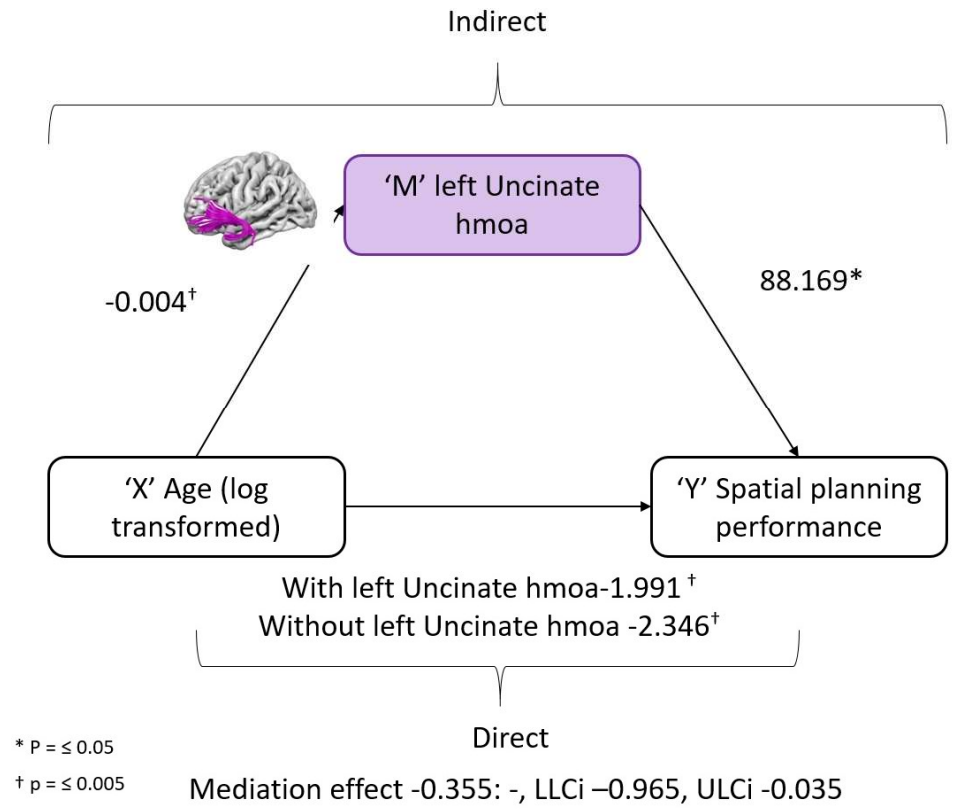


Figure 71 Mediation model of effects of left uncinate HMOA on age-related changes in spatial planning

For the paired associate's task, five tracts were identified as appropriate to be included in mediation analysis, the left cingulum, left IFOF and all three segments of the right SLF system. Of these, only two tracts, the left cingulum and left IFOF were candidate tracts for mediation analysis.

For the left cingulum, results showed that as per the logic of Baron and Kenny, there were significant relationships for all paths a, b, &c, and when comparing path c and c', the coefficient and significance of the relationship between age and paired associates performance decreased to some degree (see table 23) when including the mediator (left cingulum hmoa) in the model. However, the mediation effect was only partial. When considering the indirect effect as calculated using a boostrap confidence intervals method there was a significant indirect effect of age on paired associate's performance through the left cingulum HMOA, b = -0.580, [BCa -1.253, -0.153]. This was a reasonably small to medium effect, r^2 = 0.0678, SE .0373 [BCa .0151, .1728].

Table 23 Significance of paths a, b c & c' when considering age, paired associates and left cingulum hmoa

	Coefficient	**SE**	**Significance**
Path a (Age & left cingulum hmoa)	-.0044	.0013	.0006
Path b (left cingulum hmoa and paired associates performance)	130.5717	46.2843	.0060
Path c (age and paired associates performance)	-1.802	.5527	.0015
Path c' (age and paired associates performance controlling for left cingulum hmoa)	-1.2301	.5695	.0337

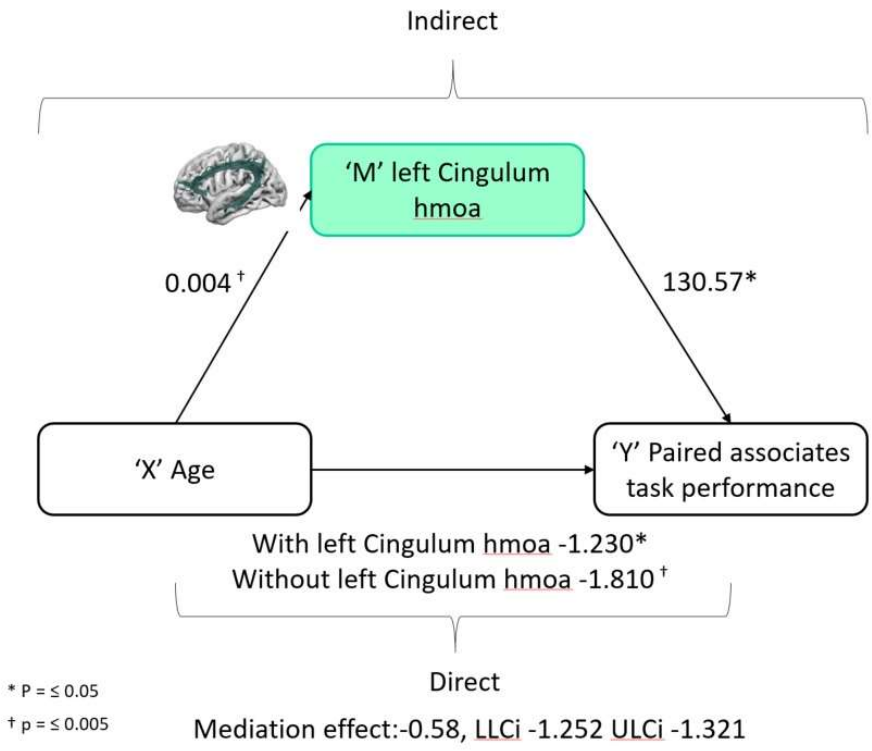


Figure 72 Mediation model of effects of left cingulum HMOA on age related changes in paired associate's performance

For the left IFOF, results showed that as per the logic of Baron and Kenny, there were significant relationships for paths a, b & c and when comparing path c and c', the coefficient and significance of the relationship between age and paired associates performance became non-significant when including the mediator (left IFOF hmoa) in the model. This was a full mediation effect. When considering the indirect effect as calculated using a boostrap confidence intervals method there was a significant indirect effect of age on paired associate's performance through the left IFOF HMOA: (b = 0.696, BCa -1.526, -0.051). This was a reasonably small to medium effect: r^2 = .0812, SE .0382 [BCa .0216, .1737].

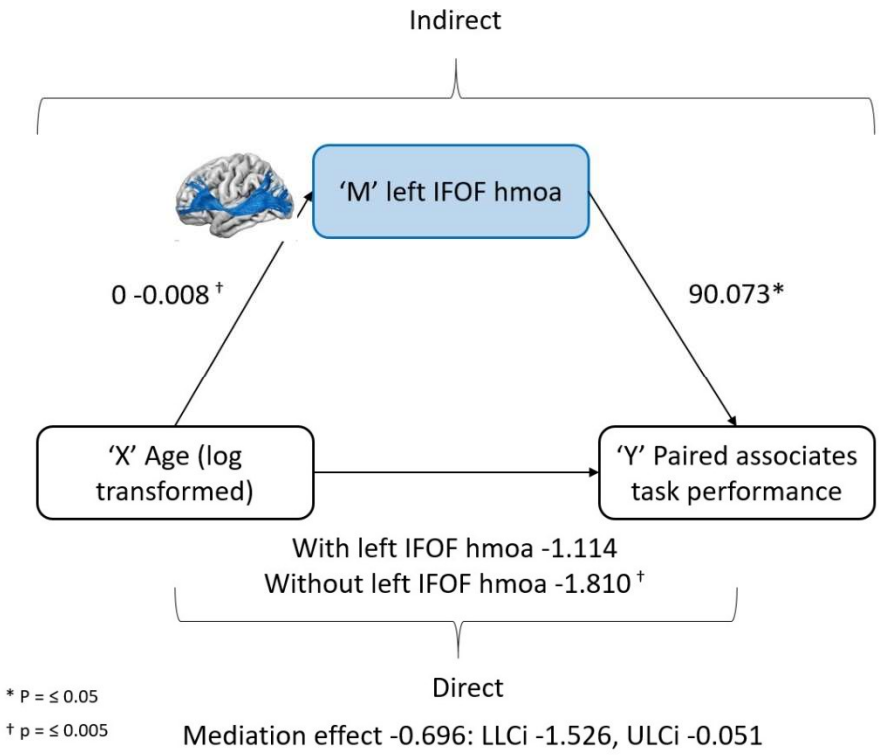


Figure 73 Mediation model of effects of left IFOF HMOA on age related changes in paired associate's performance

Table 24 Significance of paths a, b, c & c' when considering age, paired associates and left IFOF hmoa

	Coefficient	**SE**	**Significance**
Path a (Age & left IFOF hmoa)	-.0077	.0014	.0000
Path b (left IFOF hmoa and paired associates performance)	90.0729	40.6616	.0295
Path c (age and paired associates performance)	-1.8102	.5527	.0015
Path c' (age and spatial planning performance controlling for left IFOF hmoa)	-1.1141	.6250	.0783

Chapter 6 Discussion

The aim of this observational study was to find out how microstructure of frontal white matter tracts might influence executive decline in healthy ageing. Executive function itself is a complex construct and the neurobiological changes of ageing are equally complicated. In order to address this, three clear research questions were asked concerning subcomponents or processes of executive function: attention, working memory and planning. The opportunity was also taken to include some additional frontal lobe tracts and behavioural measures of executive function and episodic memory in further exploratory analysis.

Behavioural measures were taken from a computerized battery of tasks. Measures of tract microstructure were obtained by delineating specific pathways using new semi-automated dissection methods. These methods were tested and with a few exceptions were shown to produce good to excellent reliability of tract volume and HMOA across both young and older adult age groups. Results from the regression, correlation and when appropriate, mediation analysis provided at the time of writing, the first descriptions of ageing trajectories for the FAT and SLF. They were unable to demonstrate significant mediatory roles in executive decline with age of any of the tracts of interest identified from the literature (cingulum, IFOF and SLF system). Instead, exploratory analysis highlighted potentially more prominent roles of the uncinate in EF and the cingulum and IFOF in episodic memory than originally supposed.

These findings will now be discussed in more detail in the following six sections. Section 6.1 provides a brief summary of the overall outcomes from manual and semi-automated dissection protocol reliability analysis described in detail in Chapter 4. Sections 6.2 – 6.4 discuss the results of the three research questions. Each of these sections provides a description of ageing trajectories of the relevant task and white matter pathways of interest and then discusses findings from the analyses designed to probe potential mediation interactions between candidate tracts, age and task performance. Section 6.5 discusses five themes observed from the exploratory analysis including ageing trajectories of the corpus callosum, FAT and uncinate, additional relationships between tracts and the cognitive process of attention, neural correlates of the self-ordered search and paired associates and planning tasks. Lastly, the summary section 6.6

reflects on these findings in the context of relevant psychological and neurocognitive models. It then discusses limitations of the study and potential next steps.

6.1 Reliability of dissection protocols in young and older adults

A detailed review of manual and semi-automated dissection methods for all tracts of interest included in this study was conducted. When using manual dissection protocols, a general trend of decreased reliability in volume measurements with age was noticeable for 13 of the 19 tracts / segments but these were not statistically significant. Counter intuitively a slight trend of slightly more than half the tracts (11 of the 19) *increased* in HMOA with age, although the differences were again were small and not significant. This provided assurance that these protocols could be reliably used across participants of across the adult lifespan.

While HMOA reliability is generally good, the third segment of the corpus callosum, the right FAT and right IFOF demonstrated poor volume or HMOA reliability scores in at least one of the age groups and were therefore removed from further analysis.

Further discussion regarding these results can be found in section 4.5

6.2 Ageing, white matter and selective attention

In answer to the first of three research questions 'Does microstructure of the cingulum play a mediatory role in age related declines of selective attention in healthy adults?', no evidence was found to support a role for this tract age-related performance decline. Separate significant age-related declines of task performance and of HMOA of the left cingulum were observed. The right cingulum demonstrated a trend towards age related decline, but this was not significant. There were no significant correlations between either the left or right cingulum with task performance. From exploratory analysis however, a significant relationship between left IFOF HMOA and this task was observed (this is discussed further in section 6.5.2).

6.2.1 Ageing patterns of the cingulum

It is notable that only the left cingulum exhibited a significant age related decline in HMOA and that this was relatively mild in comparison to other tracts included in the study. (Lebel et al., 2012) describes the cingulum as being one of the latest tracts to peak in FA (at approx. 42.2 years of age) and observed that the corresponding decreases in FA were relatively small (a drop of 5%). However, they did not separate out their results between left and right hemispheres, nor did they divide the cingulum into smaller segments. Other studies that have examined the cingulum and how it is changes with age found similarly subtle results; (Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2008) observed no significant differences between left or right cingulum in a group of 38 healthy adults aged 18 to 88 years of age. They could not identify a significant decrease in FA but did find a weak increase in mean diffusivity. Three separate studies on the other hand (Martensson et al., 2018; Sibilia et al., 2017; Sullivan, Rohlfing, & Pfefferbaum, 2010b), found decreases in FA with age in the anterior and superior segments of the cingulum/cingulate bundle, but not in the more inferior/para-hippocampal regions. Alternate to these findings, a more recent study of 90 healthy subjects aged between 20 and 78 years of age segmenting the cingulum into five sections found significant age-related changes to FA in anterior and para-hippocampal parts of the tract (Jang et al., 2016b). Overall, the theme from the literature is that age related changes to the cingulum, if they do exist, are subtle, and that there is a possibility these changes may vary slightly between hemisphere and segment although these are not yet firmly established observations. The findings from this study seem to broadly align with this theme.

6.2.2 Neural correlates of selective attention

In the study by (Hampshire et al., 2012), the color-word remapping task demonstrated a closer affinity with the cortical network of reasoning, which included activation of the inferior frontal sulcus, inferior parietal cortex, dorsal anterior cingulate and pre-SMA. Due to the clear role of the anterior cingulate in this network, the absence of the cingulum's involvement in this task is therefore unexpected. One possible reason for this could be with the way the cingulum was delineated. Instead of separating out the cingulum into anterior, dorsal and para-hippocampal segments, the entire tract was included in analysis. (Takei et al., 2009) investigated how changes to microstructure of pregenual and dorsal segments of the cingulum impacted on performance of

the Stroop task in patients with Schizophrenia and age matched controls. They found that increased mean diffusivity of the dorsal segment of the cingulum was significantly associated with slower reaction time in the Stroop task in the patient group. Similarly, in their study of patients with end stage renal disease (ESRD) and age matched controls, (Mu, Gu, et al., 2018) investigated how the relationship between a marker of kidney disease (haemoglobin levels) interacted with white matter microstructure of the cingulum, and how this was associated with reduced cognitive control. They found that anterior regions of the cingulum microstructure mediated the impact of haemoglobin on cognitive control. However, to suppose that segmenting the cingulum when testing its role in selective attention may clarify matters could still be too simplistic. In their study of 202 healthy older adults (over the age of 60 years) (Bettcher et al., 2016) found significant correlations between FA of the whole cingulum, and corpus callosum and performance of a group of tasks (including the Stroop task) representing set-shifting and inhibition. Conversely, (Hirsiger et al., 2016) could not find any involvement of cingulum microstructure in a composite score measuring executive function (of which a Stroop task was included). The discrepancies across the literature, and between the literature and results from this study may in part be due to differences in methodologies. (Bettcher et al., 2016; Hirsiger et al., 2016) focused on healthy older adults, whereas (Mu, Chen, et al., 2018; Takei et al., 2009) focused on younger adult patients and aged matched controls. Some studies used deterministic tractography while others used probabilistic approaches or tract based spatial statistics (TBSS) to measure white matter microstructure. Importantly, in this thesis the measure of microstructure used (HMOA) had been confirmed as robust and reliable across the different ages of participants. The behavioural measures also differed from study to study, with some being part of averaged scores across a group of tests, others using the Stroop task as a single measure. None of the studies applied spherical deconvolution to their imaging data, nor did they include healthy adults across the full (young to older adult) lifespan as this study did. Next steps to further probe the role of the cingulum in selective attention would be to conduct a systematic review mapping function to each segment of the cingulum, and expanding on work already done by (Jang et al., 2016b; Martensson et al., 2018; Sullivan et al., 2010b) test how different segments of the cingulum may influence cognitive decline within this data set.

6.3 Ageing, white matter and spatial working memory

In answer to the second research question, 'Does microstructure of the bilateral cingulum, IFOF and SLF system play a mediatory role in age related declines of spatial working memory in healthy adults?' no evidence was found to support a role for these tracts in age related decline when performing the spatial span task. A trend towards a significant relationship between HMOA of the left cingulum and task performance was observed but did not survive correction for multiple comparisons. A significant correlation between left IFOF HMOA and spatial span performance was observed, but subsequent mediation analysis did not reveal any significant role in age related working memory decline.

A significant decline in performance of the spatial span task was observed with increasing age. Significant age-related declines were also observed in HMOA of the left IFOF, left SLF III, and all three segments of the right SLF system. [The left SLF I and SLF II did not exhibit age related decline with HMOA. Due to issues with the reliability of HMOA measures using the semi-automated dissection software, the right IFOF was excluded from analysis].

6.3.1 Ageing patterns of the IFOF and SLF system

[Aging trajectories of cingulum HMOA are already discussed in section 6.2.1].

Age explained 25% of HMOA decline for the left IFOF, which was the largest effect across all tracts included in this study. (Lebel et al., 2012) described the IFOF as one of the earliest association tracts to mature, with the greatest level of change across the lifespan – with increases of 12% up to peak FA and a 11% decrease afterwards.

For the SLF system, there was a lack of age-related changes in HMOA for the more medial and dorsally positioned segments, particularly in the left hemisphere (e.g. SLFI). This cannot be directly compared to changes of the SLF described by (Lebel et al., 2011) as this research group while using the term 'SLF' in fact measured the arcuate fasciculus (the tract described having a fronto-parieto-temporal trajectory curving around the sylvan fissure). Although there are similarities or even an exchangeability between the anterior (fronto-parietal) segment of the

arcuate (Catani & Jones, 2005) and the SLFIII, Lebel et al do not separate out the tract into this level of detail.

Additionally, the SLF system on the left hemisphere overall seems to have a reduced age-related decline of HMOA compared to the right. This intriguing split trajectory of age-related decline for the SLF system is thought to be novel at the time of writing. The left hemisphere, and in particular the SLFIII or anterior segment of the arcuate is associated with the function of language. Language, as previously mentioned, is reasonably stable across the adult lifespan (Hampshire et al., 2012).

Another observation of the SLF system is a possible medio-dorsal to ventro-lateral gradient of age-related decline particularly for the right hemisphere. Bilateral SLFI exhibit either very little or no age-related decline in microstructure and are positioned at the most medial-dorsal point. In the right hemisphere, the HMOA-age related decline gradually increases with each tract as they move laterally and ventrally. In the left hemisphere, the SLFII remains more aligned to the SLFI. It is worth noting the informal observation in Appendix F regarding the variability of alignment of SLFII's location. In the data set used for dissection protocol reliability it was shown that in the left hemisphere for more than half of individuals (56%) it was difficult to differentiate between SLFI and SLFII they were so closely situated together. Whereas in the right hemisphere this occurred in only 6% of cases. This gradient pattern is contrary to observations made by (Sullivan, Rohlfing, & Pfefferbaum, 2010) who proposed an inferior - superior gradient when examining several different white matter tracts.

One would recommend examining the exact anatomy of the SLF system in more detail for future studies. One could speculate for example that the dorso-medial to ventro-lateral gradient of age associated decline might be related to the positioning of the cerebrovasculature. For example, larger vessels are positioned closer to SLFIII tracts, proximal to the sylvian fissure [left middle cerebral artery vessel and ascending frontal, precentral and central branches] compared to the more modest cerebrovasculature surrounding the medial/dorsal SLFI.

6.3.2 Neural correlates of spatial working memory

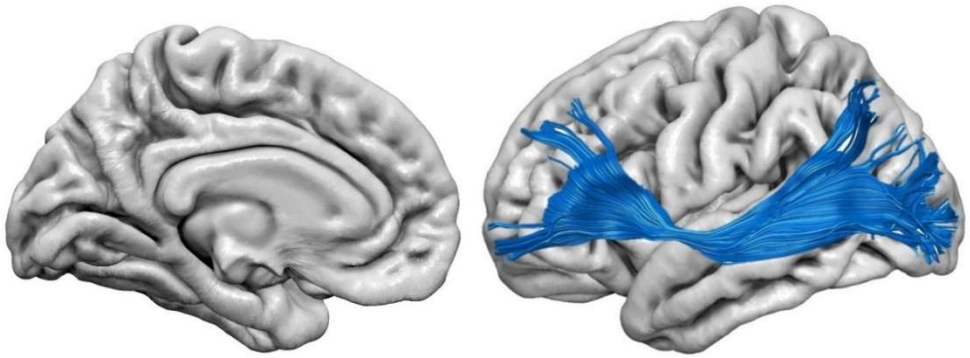


Figure 74 Left IFOF HMOA correlates with spatial span performance in exploratory analysis

Of the three tract systems identified in the original research question, only the left IFOF displayed a significant correlation with spatial working memory performance. A correlation between the left cingulum and task performance was observed, but this did not survive correction for multiple comparisons. None of the SLF segments correlated with this task.

In the literature, preliminary evidence of involvement of the SLF system seems promising. Lesion and studies have identified a connection between damage to the frontal lobe and working memory deficits (Owen, Downes, Sahakian, Polkey, & Robbins, 1990). A later PET imaging study identified activation of frontal and posterior parietal lobes in the right hemisphere in a group of participants conducting working memory tasks (Jonides et al., 1993). Similar regions were identified as important for working memory in a group of stroke patients in a later study (van Asselen et al., 2006). This work was expanded by (Chechlacz et al., 2014) in their study investigating neural substrates of the Corsi Block Tapping task in a patient group with left and right lesions. They found significant associations between reduced performance for spatial working memory and damage to posterior parietal regions, including the parietal – temporal (posterior) segment of the arcuate. Using tract-wise lesion deficit analysis they observed a relationship between disconnection of the ILF, IFOF and SLF system and reduced spatial span capacity. In addition recent publications describing positive outcomes of cognitive training on working memory observed microstructural improvements of the cingulum and SLF (Metzler-

Baddeley et al., 2017) although a significant direct correlation between function and tract measures was not obtained.

Much of this research has drawn upon patient groups with serious damage to varying amounts of brain tissue, cortical and sub cortical. The exceptions are the PET study (Jonides et al., 1993) which included 18 healthy subjects, and the work by (Metzler-Baddeley et al., 2017) which included 48 young healthy adults. For these studies, fronto-parietal involvement was alluded to, but the results were not quite as conclusive as those involving patient groups. One could speculate that in healthy adults, fronto-parietal pathways such as the SLF are required as part of a wider network and as such they do not present as the primary tracts of importance. This may in part explain why no segment of the SLF demonstrated significant correlation with spatial span scores in this study.

Regarding the cingulum, there is less evidence of its involvement in working memory in the literature. (Oberlin et al., 2016) did find that changes in microstructure of several tracts, the anterior corona radiata, anterior internal capsule, fornix, corpus callosum and cingulum mediated the relationship between improved cardiorespiratory fitness of a group of older healthy adults and spatial memory performance. (Metzler-Baddeley et al., 2017) identified only the para-hippocampal region of the cingulum as demonstrating improved microstructure after working memory training. In this study, cingulum microstructure did demonstrate a trend towards involvement in this task, but this did not survive multiple comparisons.

The involvement of the IFOF is intriguing. It's anatomical position aligns partly with the frontal operculum, one of the regions in with the short-term memory network described by (Hampshire et al., 2012) of which this task was associated with. There are also some regions of the pathway that extend up to anterior dorsolateral areas, which are well established in the literature for their involvement in working memory (see section 2.5.1 for a more detailed description of IFOF anatomy).

Alongside other long range association pathways the IFOF has already been identified as associated with working memory in the lesion study by (Chechlacz et al., 2014). They raised two points that are of particular relevance here. First, they suggested that particularly of their patient group (of whom some also suffered spatial neglect), it was important to consider the potential overlap between attentional and working memory processes. Second, they emphasised the importance of right posterior brain regions (posterior parietal and occipital cortices) in spatial working memory performance. There is an obvious discrepancy here between the reporting of right cortical regions being of interest and the results from this analysis identifying the left IFOF being involved. However, in their paper (Chechlacz et al., 2014), found that while the posterior cortical regions were localized in the right hemisphere, disconnection of long-range association tracts (including the IFOF) involved both hemispheres. Additionally, the absence of the right IFOF in the analysis for this study means it is not possible to interpret any patterns of lateralization in relation to this tract at this stage. So, although a potential lateralization of the IFOF cannot be explored further from these results, the observation that the IFOF connects posterior parietal and occipital regions with the frontal lobe can be discussed.

The importance of posterior brain regions in working memory and attention was recognised by (Furey, Pietrini, & Haxby, 2000) who examined the impact of cholinergic enhancement (through the administration of physostigmine) on activation levels in the DLPFC and occipital lobes during an fMRI working memory task performed by seven young healthy adults. Cholinergic enhancement seemed to increase activation levels in the extrastriate region of the occipital cortex and decrease activation levels of the anterior DLPFC. They suggested that such changes in regional activity could be associated with improved encoding of information in the occipital lobe, which in turn reduced the need for the DLPFC to effect control of maintaining the information online. It was proposed that an enhanced selective attention enabled more focused encoding of relevant stimuli and less focus on irrelevant stimuli in the visual cortex. While (Chechlacz et al., 2014) could not identify clear correlations between grey matter regions of the anterior prefrontal cortex the IFOF does partly connect this region with other cortical termination points. In addition, the role of the IFOF in attention is becoming more evident in recent literature (Chechlacz, Mantini,

et al., 2015; Chen et al., 2016; Vaessen, Saj, Lovblad, Gschwind, & Vuilleumier, 2016) and will be discussed further in section 6.5.2.

6.4 Ageing, white matter and planning

In answer to the third research question asked, 'Does microstructure of the bilateral cingulum IFOF and SLF system play mediatory roles in age related declines of spatial planning ability in healthy adults?', no evidence was found to support a role for any of these tracts in age related decline of planning ability using the spatial planning task. However, exploratory analysis identified a tract outside of the original hypothesis, the left uncinate that did demonstrate partial mediatory effects on changes in planning performance with age.

6.4.1 Ageing patterns of the cingulum, IFOF and SLF

The ageing trajectories of these tracts have already been described in section 6.2.1 and 6.3.1

6.4.2 Neural correlates of planning

No tracts included in the original research question were shown to be associated with the spatial planning task. The right SLF did show a significant correlation (0.248) but this did not survive multiple comparisons.

(Hampshire et al., 2012) reported activation patterns in the dorsal anterior cingulate and ventrolateral and parietal cortices in their reasoning network. White matter tracts underpinning these regions would be the cingulum, possibly the IFOF and ventral segment of the SLF system (SLF III). Furthermore, additional evidence from neuroimaging studies suggests the involvement particularly of fronto-parietal regions (Trujillo et al., 2015; van den Heuvel et al., 2003) in planning ability. The SLF system is uniquely placed to connect both dorsolateral and ventrolateral regions of the prefrontal cortex with the parietal lobe (Thiebaut de Schotten, Dell'Acqua, et al., 2011). Despite this, only the right SLFIII exhibited any association with the task, and this correlation did not survive multiple comparisons. These results were unexpected.

The spatial planning task represents many different cognitive processes. It requires the internal visualisation of the current and goal states, the ability to hypothesise intermediate steps and sequence them in order to achieve the goal state, and monitoring and cognitive flexibility to check

progress towards the goal is being made and to implement any changes to the plan if required. It also requires the ability to retain given rules and adhere to them within the context of completing the task. Functions such as attention, working memory, visuospatial processing, inhibition and cognitive flexibility are all required in order to perform well in this task. It is perhaps the complex integration of different cognitive processes involved in this task that might in part explain why no clear group of white matter pathways were definitively associated with it. In addition, while encapsulating a broad range of cognitive components, scores of the spatial planning task are limited to a single scalar variable incorporating the minimum number of moves required for each trial multiplied by the total number of moves actually made. A single measure for such a complex set of processes perhaps distils out crucial information that could better characterise the planning process. While certainly sensitive to subtle age-related decline, and larger differences between patient cohorts and healthy controls, this task may not translate well for use with structural neuroimaging methods.

6.5 Additional findings from exploratory analysis

6.5.1 Patterns of aging for the corpus callosum, frontal aslant tract and uncinate

The corpus callosum presented with an anterior-posterior gradient of age-related decline, i.e. that is the most anterior segments were sensitive to age while the more posterior segments were not. This reflects previous findings from (Abe et al., 2002; Pfefferbaum et al., 2000). However, while following the afore-mentioned trend, other research has found a small but significant decline in microstructure with age in the posterior corpus callosum ($r = 0.49$, $p = <0.001$) although this was reduced compared to the most anterior segment ($r = 0.69$, $9 = > 0.001$) (Voineskos et al., 2012). There were several differences between methods of this study and those of (Voineskos et al., 2012). These researchers conducted their analysis using FA as an index of microstructure and they divided the corpus callosum into five segments (Hofer & Frahm, 2006). They had a sample group of 48 healthy right-handed subjects between 22 to 81 years of age (mean 49 ± 17). At the time of writing a replication of these findings was not found. Perhaps other larger studies or pooled data across several studies may allow for replication or a better understanding of this anterior-posterior gradient and how it presents itself in this commissural tract.

The left frontal aslant tract (the right was excluded from analysis due to issues with reliability of measures using the semi-automated dissection method) demonstrated small (6%) significant age-related decline of HMOA. Changes of microstructure across the lifespan has not previously been reported in this intra-lobar tract.

Ageing patterns of the cingulum, IFOF and SLF have already been described in previous sections.

The uncinate, while not included in the original research question, was observed to have potential relevance to this task in results generated during exploratory analysis and so a brief description of its ageing trajectory seems appropriate to add at this point. Both the left and right uncinate demonstrated significant declines in HMOA with age, although the right uncinate had a steeper decline than the left. (Lebel et al., 2012) observed that the uncinate was one of the later pathways to reach peak FA at 35.8 years of age (compared to for example, the genu of the corpus callosum which peaked in FA at 20.8 and the fornix at 19.5 years of age). The uncinate also demonstrated

reasonably large changes in FA over the adult lifespan (11 -1 3% increase and 6 – 9% decreases around peak FA age) (Lebel et al., 2012). As with the IFOF this is perhaps one of the tracts more sensitive to age related changes than others.

6.5.2 Neural correlates of attention

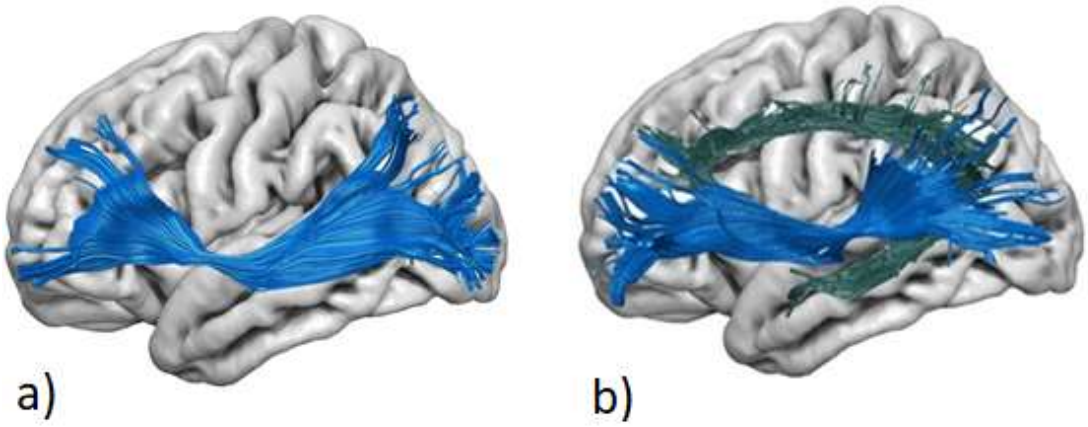


Figure 75 Neural correlates of the a) colour-word remapping and b) feature match tasks

In research question 1 the hypothesis suggested that the cingulum would play a key role in age related decline of selective attention. However, no such relationship was observed. Exploratory analysis however identified a significant correlation between HMOA of the left IFOF and performance of the colour-word remapping task and the feature match task, both behavioural measure of attention. In addition, the feature match task was also associated with HMOA of the left cingulum. In this section, the neural correlates of this second measure of attention, the feature match task will be discussed. Then the neural correlates of the colour-word remapping task will be revisited.

6.5.2.1 Neural correlates of the feature match task.

This task measures perception and selective visual attention. An individual is required to view two boxes that are situated side by side that each contain a set of complex visual stimuli. The aim is to ascertain whether or not they are the same or different. Neural correlates identified with this task are thought to be the VLPFC, frontal eye fields and posterior parietal cortex.

The anatomical connections of the cingulum do not fit closely with the cortical regions associated with this task. It does not have direct connections with the VLPFC or frontal eye fields and travels through the medial rather than lateral sections of the parietal cortex. Despite this, the reduced FA in the left cingulum has been associated with reduced attention faculties in patients with Schizophrenia (Nestor et al., 2007) while the FA in the right has been associated with attention

function in healthy young adults. The cingulum as also been associated with attention and visual-spatial processing in a group of 220 older adults (Kantarci et al., 2011) and reduced working memory capacity in patients with Multiple Sclerosis (MS) (Sepulcre et al., 2009). Attention and visuospatial processing are both functions required to complete this task.

As previously mentioned, the IFOF while reaching to the most anterior sections of the PFC does have branches that may connect with the rostral VLPFC and DLPFC. It has been associated with the function of visual attention and indeed damage to the left IFOF has previously been shown to impair a task that requires the copying of fine detail from a complex image (Chechlacz, Mantini, et al., 2015).

The absence of a significant relationship between this task and part or all the SLF system should be noted, particularly due to the cortical regions they connect. The SLFI & I connect regions of the superior and middle frontal gyri (BA8, also where the frontal eye fields are located) with posterior parietal regions, and the SLFIII connects the VLPFC with the parietal lobe. However, their presence is not deemed required from these data. It is perhaps becoming clearer as the relationship between white matter tracts and each task is examined, that there is not always a clear 1 -2 -1 mapping of cortical regions to white matter connections when considering functional connectivity.

6.5.2.2 A revised view of neural correlates of the colour-word remapping task

One obvious question arises when comparing these two behavioural measures. Why was the cingulum associated with the feature match and not the colour-word remapping task? It is feasible to return to an explanation already explored – that different sections of the cingulum may be involved in slightly different cognitive processes and perhaps the feature match task recruits more of these segments than the colour word remapping task. This is supposition however, and further investigation is required to be able to test this theory.

As alluded to in previously, the IFOF is becoming a tract of interest in the processes of attention. The IFOF does connect ventrolateral regions of the prefrontal cortex and part of the inferior parietal cortex together, linking cortical regions associated with the reasoning identified by (Hampshire et al., 2012) of which this task was aligned to. Indeed some groups have proposed that the IFOF can be segmented, and that different segments may support different functions. (Panesar et al., 2017) suggested that more lateral segments of the IFOF support the function of language, while deeper segments connecting more anterior frontal with posterior parietal and occipital regions may other functions such as goal directed navigation, sensorimotor processing, spatial perception and attention.

What is intriguing about the results of this study is the association with this task of the IFOF in the left hemisphere. Although there is evidence of right hemisphere dominance in attentional processes (Ten Brink et al., 2016; Vaessen et al., 2016) other studies have proposed there be a more subtle interplay between the two hemispheres depending on the attentional process being recruited (Chechlacz, Mantini, et al., 2015; Thiebaut de Schotten, Dell'Acqua, et al., 2011).

The idea that neural networks involved in attentional processes may be lateralized is not a new one. In their review (Corbetta & Shulman, 2002) explored the idea that different facets of attention were employed by either 'top down' processes located in dorsal fronto-parietal regions or by a salience detection system located in ventrolateral fronto-parietal areas predominantly in the right hemisphere. In a small cohort of young healthy adults (Thiebaut de Schotten, Dell'Acqua, et al., 2011) identified a relationship between a variation in the volume of SLF II between left and right hemispheres and performance of line bisection tasks. Other research groups have begun to assign different sets of tracts of the left or right hemisphere according to slightly different facets of attention. For example, in a group of 248 stroke patients damage to the left IFOF was shown to correlate with impaired performance of a task that requires the copying of fine detail from a complex image (Chechlacz, Mantini, Gillebert, & Humphreys, 2015), whereas damage to tracts in the right hemisphere (the right SLF III and long segment of the arcuate) correlated with impaired performance in subjects required to process global features. When using a different measure of several different cognitive processes within an attention based paradigm (including processing

speed, visual short term memory capacity, spatial bias and top down controlled selection) (Chechlacz, Gillebert, et al., 2015) identified the right IFOF, SLF II and SLF III in the visual short term memory component.

In this current study however, it would not be prudent to draw any conclusions about lateralization of the IFOF in relation to this task, as it was not possible to include measures of the right IFOF in the analysis. Rather, one can infer only that the left IFOF at a minimum is involved in some component of attention, likely visuo-spatial processing, possibly regarding object location.

6.5.3 Neural correlates of the self-ordered search task

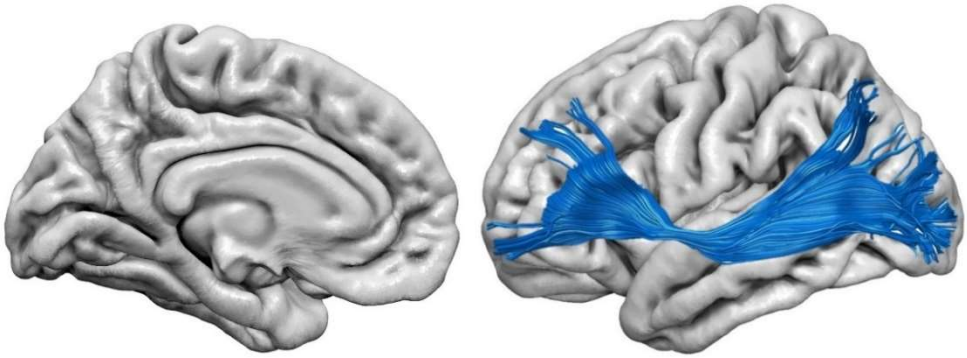


Figure 76 Neural correlates of the self-ordered search task

The self-ordered search task is thought to involve the cognitive processes of planning, inhibitory control and working memory. The neural correlates identified to date for these tasks are the DLPFC, VLPFC and medial temporal lobe. HMOA of the left IFOF demonstrated a significant negative relationship with performance scores for this task.

As previously mentioned, the IFOF connects with the more anterior regions of the DLPFC and VLPFC and travels through the internal capsule, proximal to the medial temporal lobe, cortical regions associated with this task. While predominantly measuring the aforementioned functions, attention would be an implicit requirement for task completion. Visuospatial attention is as previously mentioned something that there is preliminary evidence of IFOF involvement. This is the fourth task described so far to involve the left IFOF. One possible explanation for this is that the role of the IFOF in managing visuospatial processes involved in attention is paramount in most of these tasks due to the nature of their presentation- computerized task presented through a visuospatial interface. The exception to this is the spatial planning task, which perhaps is more sensitive to other cognitive processes and thus emphasises other tracts over the IFOF. However, the results as they stand do not provide any real evidence to support this theory. More work is required to further explore the ubiquitous nature of the IFOF using these measures.

6.5.4 Neural correlates of the paired associate's task

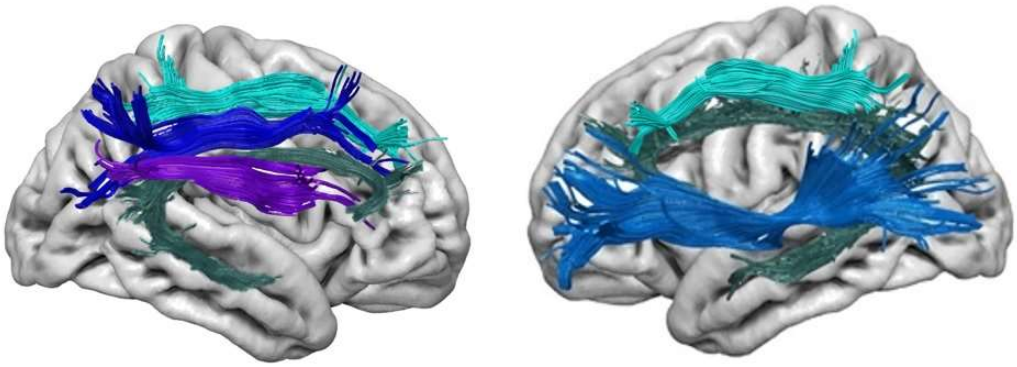


Figure 77 Neural correlates of paired associates' task

The paired associates task requires a series of different cognitive functions from encoding and retrieval to attention and working memory. Neural correlates for this task are the VLPFC, DLPFC, anterior cingulate, parietal and occipital regions and the cerebellum. White matter tracts that demonstrated a significant relationship with this task and HMOA indices were the bilateral cingulum, left IFOF, bilateral SLFI, the right SLFII and right SLFIII.

The cingulum lies medial to the cortical anterior cingulate and connects this frontal region with important para-hippocampal region in the medial temporal lobe. The frontal SLF system spreads across the DLPFC and VLPFC, connecting these regions to various areas of the parietal cortex. The IFOF connects polar regions of the frontal lobe, some anterior sections of DLPFC and VLPFC to the occipital lobes, all cortical regions associated with the task. Thus, the connective anatomy of these tracts fit well with the fMRI literature.

The cingulum has previously been associated with attention, working memory, declarative verbal memory and visuospatial processing. Attention and working memory are both functions thought to support an individual's ability to perform as task difficulty increases (Gould et al., 2003). Its position in the para-hippocampal gyrus is the same location that has been shown to be activated during active encoding and retrieval processes during a similar visual paired associates learning (PAL) task in healthy adults (Kotoula, Doyle, Simone, Mehta, & Williams, 2016).

As mentioned in the previous sections the IFOF is also associated visual attention. So too is the SLF system (Thiebaut de Schotten, Dell'Acqua, et al., 2011) although this set of pathways has not been associated with other tasks specifically measuring attention in this study. In addition, variants of the paired associates tasks have been used to assess memory impairments in healthy aging and clinical populations (Gould, Brown, & Owen, 2005; Gould, Brown, Owen, & Howard, 2003). The mediatory influence of both the left cingulum and left IFOF in age related declines in this task could allude to a decline in a combination of both strategic attentional processes and also episodic memory decline (where the para-hippocampal segment of the cingulum connects the medial temporal lobe to frontal, parietal and occipital regions).

There is more to unpack and interpret from these results than is in the scope of this current thesis. Therefore, it is recommended that new research questions be developed specifically in relation to this task to probe further the reasons for this broadly distributed structural network and why it contrasts so considerably with executive behavioural measures.

6.5.5 Revisiting the neural correlates of spatial planning

HMOA of the left uncinate not only demonstrated significant correlations with spatial planning performance, but also exhibited a partial mediatory / indirect effect (0.35, BCa CI 0.965, 0.035) on age related decline in planning. While not typically associated with planning per se, the uncinate has been associated with inhibition (Hornberger et al., 2011) attention (Singh et al., 2016) and certain forms of working memory (Charlton et al., 2010). These cognitive processes are required in part to support the completion of this task. Below these three cognitive processes are briefly discussed, and a fourth; 'verbal mediation' is suggested.

6.5.5.1 Inhibition

Could it be that the left uncinate plays a role in inhibitory processes required for successful planning strategies? Polar and anterior regions of the frontal lobe have been identified in fMRI studies as being involved in response inhibition although frequently it is the right hemisphere rather than the left that is allocated to this function (Forstmann et al., 2008; Rubia, Smith, Brammer, & Taylor, 2003). Atrophy of the orbito frontal, medial prefrontal and anterior temporal cortices have been associated with levels of disinhibition using the Hayling Test of Inhibitory Functioning in groups of patients with Fronto-Temporal Dementia (FTD) and Alzheimer's Disease (AD) (Hornberger et al., 2011). In addition changes in microstructure of the uncinate (alongside the cingulum and corpus callosum) have been correlated with behavioural variant FTD, a condition that typically exhibits disinhibition (Mahoney et al., 2014).

6.5.5.2 Attention

As previously mentioned, (Singh et al., 2016) alluded to an association between changes in uncinate FA and decreased attention ability in a small group of patients with Schizophrenia. Other research groups focused on neuroanatomical characteristics of attention and impulsivity in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) have also examined how the uncinate may be involved. For example (Shaw et al., 2015) observed a significant correlation between reduced FA in the left uncinate and greater inattention in a group of adults with ADHD. Part of the requirements of the Tower of London task is to generate in the mind's eye potential movements (sub goals) in the correct sequence to achieve the overall goal state. Sustained

attention and a level of patience is required in order to systematically review these sub goals and decide which ones will lead to the correct result and which ones need to be discarded. It may be that reduced attention influences the ability of an individual to successfully mentally navigate the more complex problems within this task.

6.5.5.3 Verbal working memory

Alternatively, (Charlton et al., 2010) observed a relationship between uncinate microstructure and working memory in a group of healthy older adults. Working memory is another cognitive component required for successful planning. The tasks used in this study were the digit span backwards and letter number sequencing tasks, which are based on verbal rather than spatial working memory. Is there a verbal rehearsal mechanism such as the phonological loop (A Baddeley, 1992) involved in supporting the planning process?

6.5.5.4 Verbal mediation

In support of the influential theory by (Vygotsky, 1962) there is some evidence in the literature that executive processes such as planning may require input from 'inner speech'. The suppression of this inner speech or verbal mediation process during completion of Tower of London tasks has been observed in several studies. In a group of 30 children (7 – 10 years of age) performance on the Tower of London task was reduced when they were asked to complete another task suppressing their 'inner speech' concurrently (Lidstone, Meins, & Fernyhough, 2010). Two other studies observing the same phenomenon in healthy adolescents and young and middle aged adults found similar results (Wallace, Silvers, Martin, & Kenworthy, 2009; Williams, Bowler, & Jarrold, 2012). As previously mentioned in Chapter 2 the uncinate has been observed to play a role in language processing. Could it be that this tract supports verbal mediation in complex executive tasks like the Tower of London?

Such questions at this stage can only be speculative. The results from this study identify the uncinate as a tract of interest in this task. We can state that these data indicate it may be associated with the way planning function declines with age. We can observe that the left uncinate

plays a stronger role in this task than its counterpart the SLFIII. However, there is still much more to be considered and explained.

6.6 Summary

6.6.1 Results in the context of psychological and neurocognitive models

What these results and observations indicate is tentative support for the ideas described by (Hampshire et al., 2012; Metzler-Baddeley et al., 2017), that executive processes do involve multiple overlapping networks. It should be acknowledged that these studies are based on functional neuroimaging whereas this one has used on structural neuroimaging methods. Functional MRI assesses ephemeral changes to blood flow in different regions of the brain. DTI examines more enduring structural networks. These are two very different measures and as such, are difficult to compare directly. Despite these differences, the results from this study do provide preliminary evidence for patterns of common (e.g. left IFOF) and different networks of white matter tracts supporting overlapping yet distinct cognitive processes.

While results from this study have shown that there are relationships between tracts and tasks and even some potential mediatory roles played by some tracts on age-related executive decline, they are insufficient to definitively support one ageing hypothesis over the other. However, in relation to the frontal ageing hypothesis (Dempster, 1992; West, 1996), some basic pre-requisites are met. All the behavioural measures of executive function did exhibit significant age-related reductions in performance. Additionally the anterior – posterior gradient of microstructural ageing of the corpus callosum replicates the work by (Abe et al., 2002; Pfefferbaum et al., 2000). However, there are two key points at which the design of this study or its results diverge from the original hypothesis proposed by (Dempster, 1992; West, 1996). Firstly, the inclusion of long-range association tracts immediately broadens the original remit of the frontal ageing hypothesis. While most of the tracts included in the study were selected because of their origination / termination points in frontal lobe, they all (except for the FAT and anterior segments of the corpus callosum) extended *beyond* the frontal lobe into other lobes. Secondly, while the changes to corpus callosum HMOA reflect an anterior-posterior gradient, the anterior segments of this commissural tract did not exhibit any correlation with any of the behavioural measures. Apart from the posterior segments of the corpus callosum (which equally did not correlate with task performance) no other posterior tracts (tracts that do not originate/terminate in the frontal lobe) like for example the ILF were included in the study. Therefore, no direct comparison can be made between the degree to

which frontal-based pathways are associated with are-related executive decline compared to those pathways that are entirely posteriorly based. If some of the tracts, like the cingulum had been segmented, this may have been possible, and indeed segmentation of the cingulum in future analyses in relation to comparison with executive function is recommended. It should also be mentioned that in other studies, the anterior region of the corpus callosum have been associated with executive processes (Bodini et al., 2013; Granberg et al., 2015) although findings in the literature regarding this relationship are still limited and mixed. Results from this study however, could not find significant correlations between ay of the corpus callosum segments and cognitive function.

When considering how the results from this study reflect on the theory of disconnection in ageing (Antonenko & Floel, 2014; Madden et al., 2017b) the following points need to be discussed. The idea behind this theory is that the long, myelinated pathways connecting different regions of the brain suffer age-related degeneration which results in a degraded ability to transmit information between distant regions of the brain. Indeed in earlier papers (Madden et al., 2009) found that changes to microstructure of certain pathways (in this case the corpus callosum) mediated age related decline in cognitive processes such as task-switching. The results from this study expand upon this principle and have found three new mediatory relationships between white matter pathways (the cingulum, IFOF and uncinate) and age-related decline in cognition (episodic memory and planning ability). However, as the theory of disconnection has matured, other neuroimaging modalities have been incorporated into more complex analyses (Bettcher et al., 2016; Fjell et al., 2017; Madden et al., 2017b) with mixed results. Some studies have supported the importance of structural changes (Bettcher et al., 2016; Fjell et al., 2017) while others have shifted to place emphasis on functional dysconnectivity as a measure of age-related cognitive decline (Madden et al., 2017b). Results from this study can then contribute in part towards the broader body of knowledge in this field and hopefully place a spotlight on certain structure and function relationships that may support and direct future research questions.

6.6.2 Limitations of the study

The design, analysis and results of this study have several limitations. Firstly, it is based on cross sectional data. Ideally, changes with age would be observed within individuals over an appropriate period of time, potentially with several different time points included in the study design to track possibly non-linear trajectories. With a cross sectional study, individual differences within the cohort cannot be reliably identified.

Secondly, the scope of this thesis was restricted to long range association pathways, one intra-lobar and one commissural tract, all with cortical connection points in the frontal lobe. It did not include the arcuate, projection pathways, other smaller intra-lobar tracts or other frontal commissural pathways. This was due in part to methodological restrictions at the time. Furthermore, of the tracts chosen for analysis, two association pathways and a segment of the corpus callosum were excluded due to issues with reproducibility using the semi-automated dissection method. This limited interpretation of lateralization effects in regard to the association tracts.

Third, adjustment for processing speed was not included in the analysis. Fourth, this study focused on microstructure measurements of specific white matter pathways and did not include measures of regional or global grey matter volumes or global white matter measures.

Fifth, the original power calculation for the study was based on a single linear regression model, and was not updated to reflect a more complex study design to support the three research questions (that is, a series of preliminary regression and correlation tests followed by potentially numerous mediation tests). To account for this, regarding the research questions, corrections for multiple tests were applied where appropriate for the pre-requisite (regression and correlation) tests. Once candidate tracts for mediators were identified, they amounted to very few per question and so correction for multiple comparisons was not required.

Lastly, the exploratory analysis did conduct several mediation analyses and there are some limitations to the methods applied that should be mentioned. Baron and Kenny’s causal steps

approach to identifying mediation is well recognised but has been criticised as being underpowered and potentially related to inflated Type 1 error rates (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). While this test was supplemented by the bootstrap BCa Confidence Interval (CI) method, this approach has more recently been described as having limitations. While originally widely used at the time of running the analysis, particularly in conjunction with the SPSS tool PROCESS, this method has also been criticised for inflated type 1 error rates. Furthermore, a reasonably low number of samples were selected (1000) which may lead to low stability regarding the CI results. This means that the results from this study should be interpreted with caution. It is recommended that should this study be repeated that an updated approach using a combination of the joint significance test and percentile confidence interval bootstrap tests be considered as proposed by (Yzerbyt, Muller, Batailler, & Judd, 2018).

6.6.3 Future directions

There are some obvious next steps to address some of the limitations mentioned above and expand upon the current study findings. Some of these next steps I will refer to as ‘staying local’ that is, using medium sized data sets to examine specific questions that have arisen from the results of this study. Other future work I will use the term ‘going big’, alluding to the opportunities that bigger, often open access data sets can provide.

6.6.3.1 Stay local

In terms of the reliability analysis, it would be beneficial to examine detailed dissection metrics and other technical output from the Megatrack application to try and identify the exact issue with tract reliability of the rostral body segment of the corpus callosum, right FAT and right IFOF. This has been discussed in more detail already in Chapter 4

A systematic review of functions aligned to specific segments of the cingulum, followed by analysis of what mediation effects each segment may be observed in age related decline of cognitive decline is recommended.

Subsequent studies could incorporate an adjustment of motor and processing speeds. Although the individual computerised tasks did not have ideal integral measures to provide this, separate measures of reaction times could be used for this purpose. In addition, incorporating other structural measures such as regional and global cortical metrics and global measures of white matter HMOA and volume is also recommended.

Lastly, the results from this study indicate further research questions could be developed to expand on the preliminary results identifying neural correlates of the paired associates task, the relationship with the left IFOF in attention processes and the role of the left uncinate in more complex executive functions such as planning.

6.6.3.2 Go big

When considering the avenue of 'go big' there are several studies that have or are in the process of collecting neuroimaging data over the adult life span. Not all include metrics on white matter or specific neuropsychological measurement of executive function, but some examples are described briefly below.

The Human Connectome Project https://www.humanconnectome.org/ (HCP) has already collated a vast data set of 1200 young healthy adults aged between 22 – 35 years of age. This work has already informed a plethora of studies using a range of different neuroimaging methods including fMRI and DTI. Some recent papers have examined specific tracts and connections (Burks et al., 2017; X. Wang et al., 2015; Wu et al., 2016) while others taken a broader view investigating for example heritability factors of FA across a range of different pathways (Kochunov et al., 2015). HCP data has also supported studies looking at ways to combine neuroimaging data with intraoperative tests to gain better understanding of brain function (Pallud, Zanello, Kuchcinski, Roux, & Muto, 2018). Analysis of multimodal neuroimaging data is becoming popular although currently the focus seems to be more on fMRI and cortical measures and inclusion of DTI methods is still relatively limited (Lerman-Sinkoff et al., 2017; Moser et al., 2017). HCP is in the process of extending its data to include older adults (aged from 36 -100+ years of age). When this becomes available, opportunities to test or replicate findings from this study may be seized,

depending on the compatibility of some of the behavioural tasks available. The HCP young adult data set does include metrics associated with some executive functions. While not exactly the same as the tasks within this thesis, they could still inform and expand upon some of the tract-task relationships alluded to in this thesis.

The ENIGMA consortium (Thompson et al., 2014) has pooled neuroimaging and genetic data across the globe. Two working groups within the consortium are investigating DTI metrics and lifespan changes. Studies focusing particular on the genetics associated with white matter are beginning to emerge. For example (Acheson et al., 2017) recently reported on reproducibility of tract based microstructural measures (FA) for several different pathways including the corpus callosum, fornix, cingulum and IFOF. They not only achieved excellent reproducibility for all tracts except the fornix and cortico spinal tract, they also documented the quality assessment procedures used to attain these results. Alternatively (Kochunov et al., 2015) used ENIGMA data to explore a number of different analytical approaches for identifying how heritable FA indices were across the brain. The type of data provided by the ENIGMA consortium might be used to further explore why some pathways are more vulnerable to age related decline than others and possibly identify genetic risk factors associated with this.

The ‘Lifebrain’ project is a collaboration that aims to pool 11 large study data sets from seven different European countries, ultimately including around 5,000 different participants. It aims to use this collective information to help infer new understanding regarding relationships between brain, cognition and mental health across the lifespan. This epitomises the ‘Go Big’ option. One of the key objectives of this operation is to ‘to yield the evidence base for development of strategy’ in relation to disease and health inequality prevention and intervention’ (Walhovd, Fjell, Westerhausen, & Nyberg, 2018).

Big data approaches promise benefits such increased power, potentially increased diversity of population samples and the economic sense of re-use of expensive data. However, there are still a number of factors to consider. One would need to carefully evaluate the methods used collating these big datasets. For example, considering outcomes from Chapter 4 it would be vital to ensure

consistent quality assurance steps are applied throughout the processing of the data. In relation to any methods using automated tractography it would be important to check that the data would be validated against 'gold standard' manual dissection methods. The same careful checks should be applied to other data processing methods such as cortical segmentation techniques using Freesurfer. With large data sets there is a risk that small errors made early on in the processing stage would be propagated through to the rest of the analysis.

Due to the resources required to generate big datasets, behavioural measures are sometimes limited or restricted in number and may not always be available to address a particular hypothesis. However, they can provide opportunities to answer questions it has not previously been possible to address with smaller data sets. (Sejnowski, Churchland, & Movshon, 2014) explore the idea of comparing the small 'vertical' data set approach which they describe as 'where single techniques are used to address single problems' to large 'horizontal' data approaches, described as 'where data is integrated across a broad range of technologies and populations to address multiple problems'. Thus in order to use big data well, one must not simply think in terms of increased quantity, but also in maintaining quality using appropriate methods and adapting questions and developing new analytical approaches (e.g. new algorithms, machine learning) to best access the answers to these questions [Bzdok, 2016].

Specific examples of how such big data could expand upon the results produced by this study would be potentially to use data form the HCP project to replicate tract / function relationships such as the IFOF's role in attention and the uncinate's role in planning in young and older adult cohorts using similar behavioural measures. Alternatively, collaborations such as the Enigma consortium could enable questions around which phenotypic or genetic factors that may moderate age related decline in white matter and cognition.

6.7 Conclusion

This study has provided an examination of 14 association and intralobar tracts and an anterior segment of the corpus callosum, all of which are associated with the frontal lobe and has identified key relationships between changes in microstructure and decline in executive and paired associate learning abilities with age. Results from this study provide potential regions of focus for future investigations to deepening our understanding of the neural correlates of executive function.

It provides first-time assessment of direct relationships between components of the SLF system and certain forms of executive function and produced microstructural ageing trajectories of the FAT. It has highlighted a potentially more prominent role in executive function than originally supposed for the IFOF and uncinate.

Further work is required to consolidate areas of this study. There is a need for refinement of the semi-automated methodology in partnership with dissection protocol revisions. Broader observations of the anatomy of the SLF system are also required. Replication of these results in separate data sets is strongly recommended.

Potential application for this knowledge could be to examine whether or not factors that promote resilience in aging also correlate with more stable microstructural trajectories of pathways of interest. Alternatively, other work streams could be focused on comparing healthy groups with patient groups of differing executive dysfunction to further probe the dynamics between white matter and behaviour. Finally, with the growing expertise in multimodal imaging, new research should also focus on combining our understanding of how cortical and sub cortical regions and the pathways connecting them interact and integrate into a functional unit. Ultimately the more we know, the easier it will be to identify potential mechanisms to support healthy aging or provide appropriate diagnosis and treatment for those that need it.

Chapter 7 References

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Appendix A Literature search

7.1 Tractography protocol reliability (hand search)

A hand search was conducted resulting in the selection of 18 articles for inclusion in the thesis Chapter 4.

7.2 Executive function, white matter and ageing

7.2.1 Search parameters 2013

The first search concerning the subject of executive function, white matter and ageing was conducted in (2013) using Science Direct. Keywords used were “brain, brain ageing, brain aging, brain anatomy, brain volume, white matter, grey matter, frontal lobe, cognition, executive function, attention, concentration, planning, working memory”

Inclusion Criteria: No restrictions were placed on search dates; Publications in English, inclusion of healthy adults (over 18 years of age) only,

Exclusion Criteria: Studies focused primarily on children; studies focusing on a pathology/ disease rather than healthy controls; studies with a focus on genetic or cellular mechanisms, animal or pre-clinical studies.

Studies selected: A total of 41 articles were included in literature review for the PhD Upgrade report.

7.2.2 Search parameters 2018

The search was conducted using PubMed and Science Direct. Keywords used were “executive function, cognitive control, attention, working memory, planning, problem solving, decision making, Tower of London, Corsi block tapping, Stroop, white matter, DTI, Diffusion Tensor Imaging, Diffusion Weighted Imaging, DWI, Fascicles, Connections, Pathways, Spherical Deconvolution, SD, TBSS, Brain.

Inclusion Criteria: Articles published before June 2018 were included; publications in English, inclusion of adults (over 18 years of age), inclusion of healthy control participants.

Exclusion Criteria: Studies focused primarily on children; studies with a focus on genetic or cellular mechanisms, animal or pre-clinical studies.

Studies selection process: Following similar screening methods described below, of approximately 1150 publications identified from the search, 365 were included in the thesis.

7.2.3 Search parameters 2019

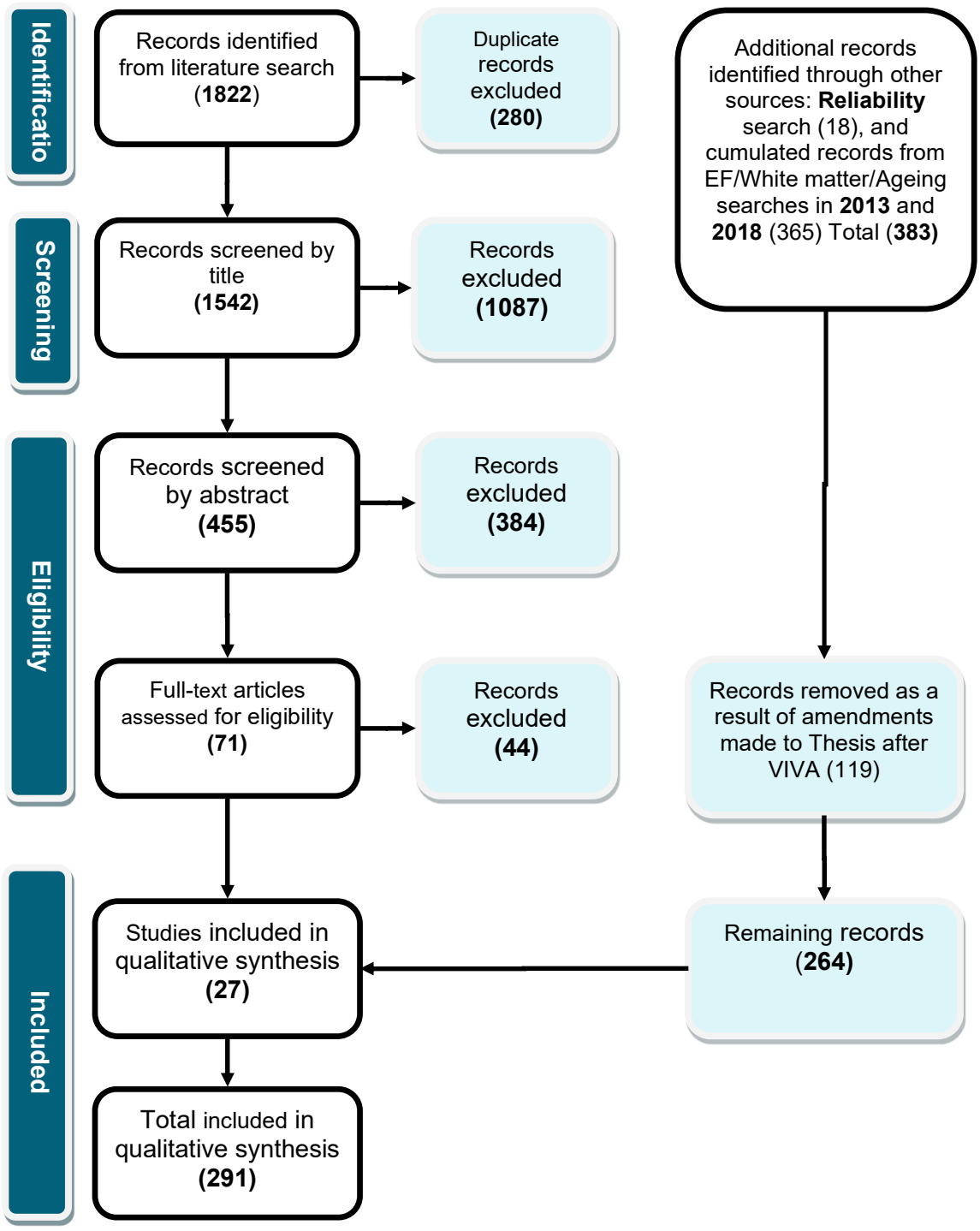
The final search was conducted using PubMed, Scopus and OVID. Keywords used were "executive function, cognitive control, attention, response inhibition, cognitive flexibility, working memory, planning, problem solving, decision making, tower of london, corsi block tapping, stroop, white matter, DTI, diffusion tensor imaging, Diffusion weighted imaging, DWI, fascicles, connections, pathways, spherical deconvolution, SD, TBSS, brain.

Inclusion Criteria: Search dates were restricted to 1st January 2013 – 31st March 2019.Publications in English, inclusion of adults (over 18 years of age),

Exclusion Criteria: Review articles, case reports, studies focused primarily on children; studies with a focus on genetic or cellular mechanisms, animal or pre-clinical studies.

Study screening process: A total of 1822 records were identified in this search, of which 280 were duplicates. From the remaining 1542 records, 1087 were removed after a brief title check. 453 abstracts were then checked, of which 71 were selected to be read in full. Of the remaining records, 27 were deemed of relevance and added to the literature referenced in the current study. (It should be noted that as a result of amendments made on this Thesis between the 2018 and 2019 search, some records were removed while other new records added).

Literature Search Flow Chart



Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 79 Literature search flowchart using PRISMA approach

Appendix B Other models of executive function

7.3 Executive function

7.3.1 Hierarchical model of EF

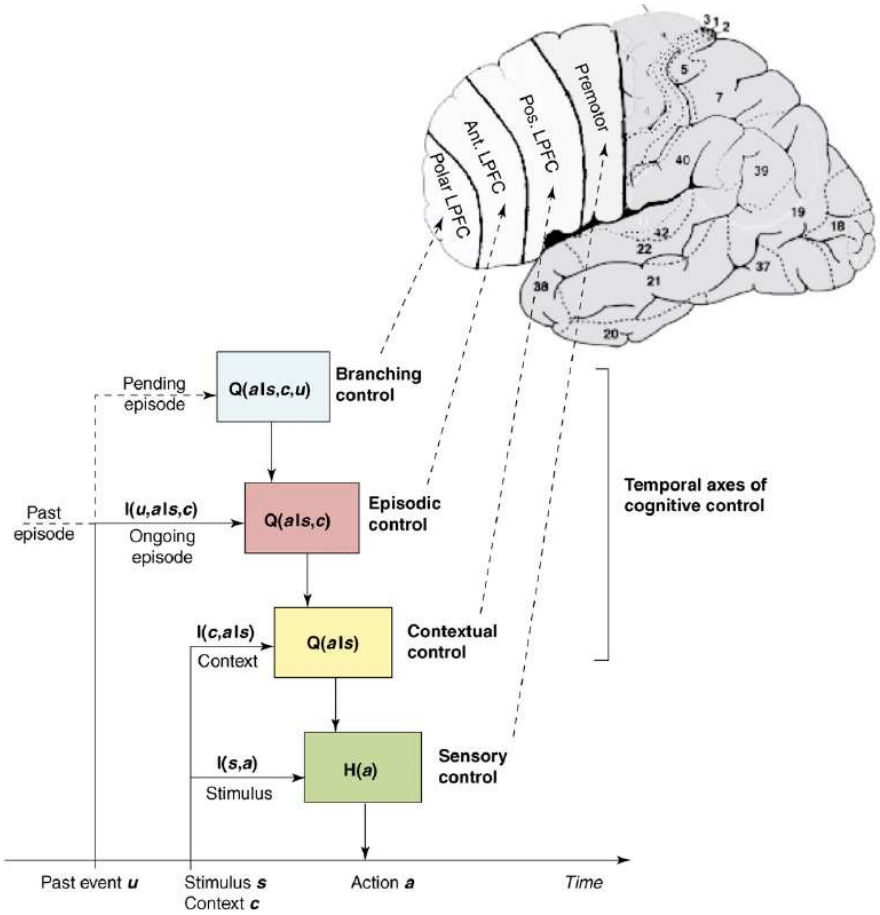


Figure 80 Information theoretical approach model, Koechlin, 2007

Based on principles from the information processing theory (Shannon, 1948), this model suggests that executive function operates through a system of computational instructions ranging from simple to highly complex. These rules enable the selection of the most appropriate response to a stimulus taking into account rules defining the current context of a situation and relevant knowledge learnt previously (episodic context) (Koechlin & Summerfield, 2007). One final component in the model is something called ‘branching’. Branching represents the ability to hold ‘online’ two or more contextual rules at the same time and to switch between them in order of their temporal priority.

The components sensorimotor control; context, episodic context and branching are mapped to different regions in the lateral prefrontal cortex following a posterior (simple information) to anterior (complex information processing) gradient (Fig. 80).

7.3.2 Perception action cycle

Fuster describes the basic units of the perception action cycle as 'cognitive memories' that range hierarchically from simple to complex and can be split into perceptual (sensory) or executive (motor, cognition and language). These memories are stored in long-term memory networks across the brain. They can be of 'sequential action past or planned' (Fuster, 2002). Fuster suggest that these components need to be organised within the temporal domain, which he terms 'temporal integration'. He posits that it is the prefrontal cortex that manages this coordination using four key processes, selective attention, working memory, preparatory set and monitoring. In his review (Fuster, 2001) attributes the more routine and overlearned 'schema's of action, as being managed by sub-cortical structures such as the basal ganglia, cerebellum and thalamus. He attributed the more complex schemas of action that have a degree of uncertainty to the PFC's.

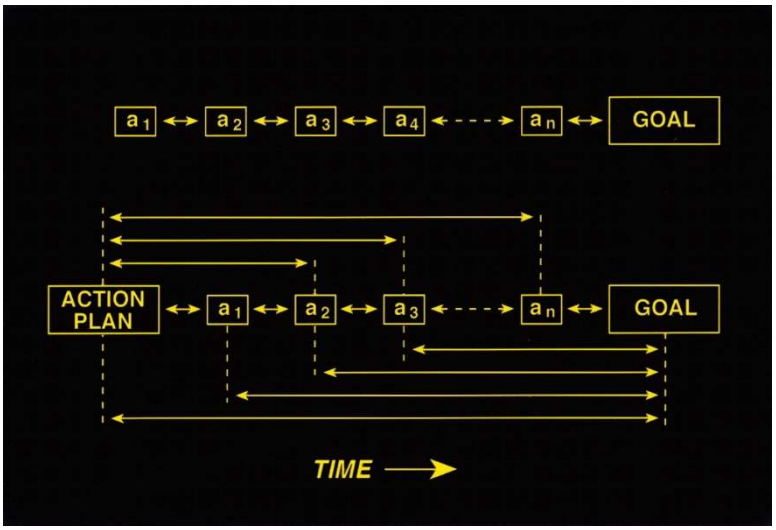


Figure 81 Sequencing of actions towards a goal (Joaquın M Fuster, 2001)

It is the process of monitoring that brings the perception action cycle into play. The perception action cycle is '*grounded on a basic biological principle: the circular cybernetic flow of cognitive information that links the organism to its environment. Sensory inputs are processed in sensory structures. The result of that processing leads to actions, which induce changes in the*

environment. These, in turn, generate new sensory signals, which feed back into the cycle and help control new action' (Fuster, 2002).

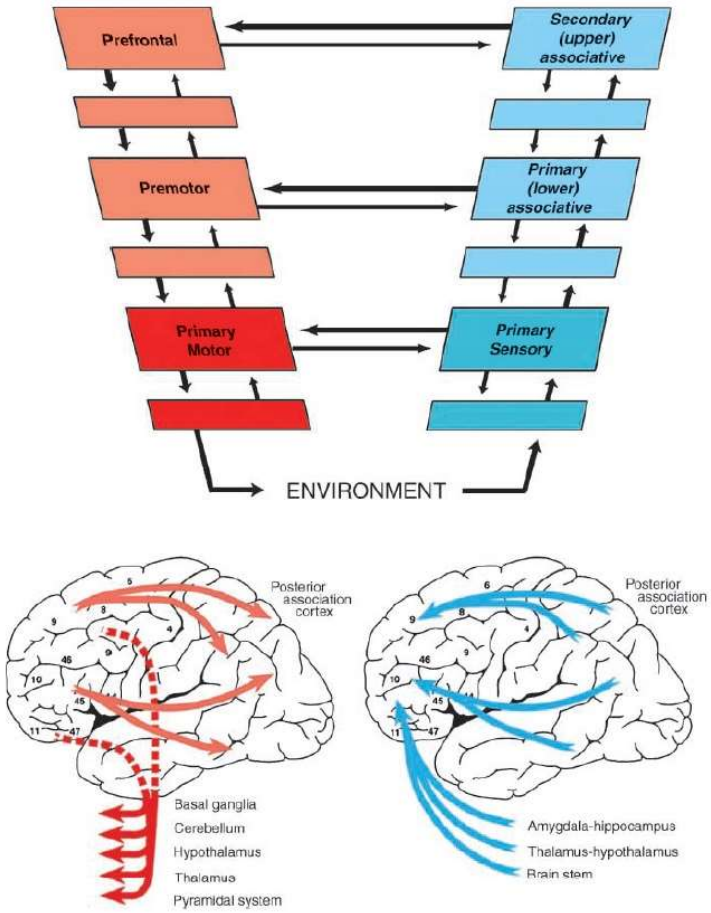


Figure 82 Schematic diagram of perception action cycle (Fuster 2009)

7.3.3 Goal neglect

Duncan's theory of goal neglect suggests that individuals have a current list of goals that they want or need to achieve at any given time. In order to achieve a goal, one must assess the gap between their current situation and the represented goal state. They then need to search through what Duncan terms a 'store of actions' to select the most appropriate ones and put them in order to achieve the goal. This order is called the 'action structure'.

Depending on the complexity of the goal a certain amount of 'means end analyses' may need to be run. That is the running of a particular scenario or set of action structures in the mind's eye to identify which combination of actions would be the most efficient approach. For new goals where

action structures have not yet been established there is a level of ambiguity as to whether the selected approach will work. During the course of carrying out the actions therefore, progress towards the goal is monitored and if corrections implemented as required. It is an iterative process. Throughout this process overall focus and control of behaviour towards achieving the goal, including inhibition of other actions less relevant to the goal is maintained. It is this overall control of behaviour to ensure goal attainment that Duncan believes is impaired in frontal lobe patients. He terms this impairment Goal neglect (Duncan, 1986). In subsequent work Duncan has also proposed that the goal directed behaviour is correlated with general intelligence or 'g' (Duncan et al., 1996). Using experimental data he also suggests that there are common regions of the brain associated with completion of goal directed behaviour using a range of different cognitive processes (Duncan & Owen, 2000).

7.3.4 Parallel organisation of basal ganglia-thalamocortical circuits

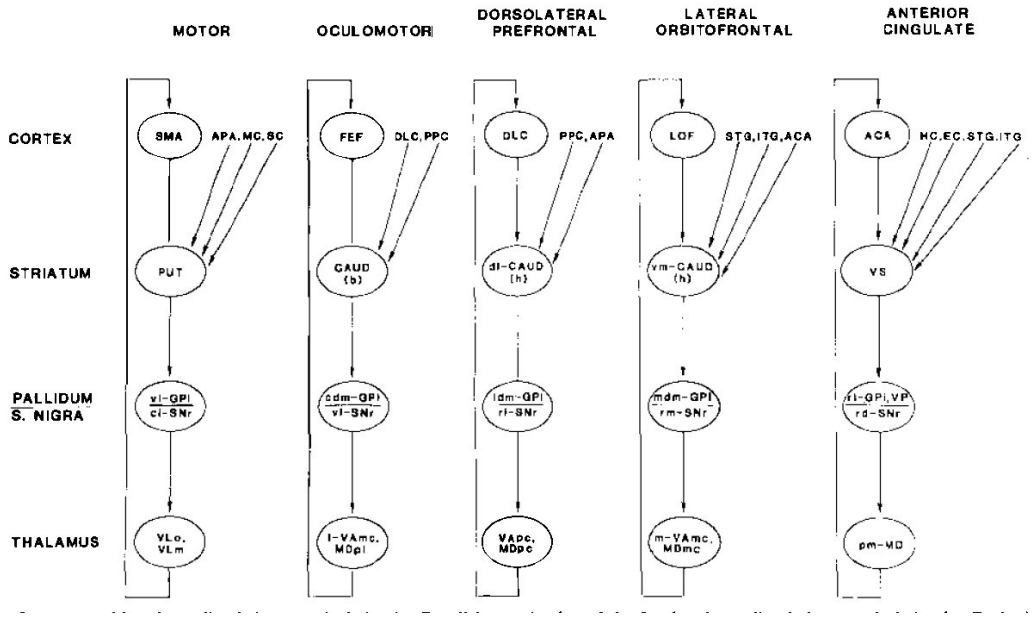


Figure 83 Parallel organisation of basal ganglia-thalamocorical circuits, (Alexander, 1986)

(Alexander, DeLong, & Strick, 1986) describes five separate loops traversing through different regions of the cortex, basal ganglia and thalamic nuclei (Fig. 83):

1. Motor
2. Occulomotor
3. DLPFC

4. Lateral orbito-frontal cortex
5. Anterior cingulate

This model emphasises the importance that sub cortical structures have in executive function alongside their cortical counterparts. The dorsolateral prefrontal circuit was described anatomically in Alexander's original paper although at the time the authors did not feel they had sufficient evidence to describe its function in great detail. Since then, this loop has been assigned to executive function (Haber, 2003).

Appendix C Other models of neurocognitive ageing

Neurocognitive aging theories	Description
Processing speed theory	The processing speed theory was initially proposed by Salthouse in his book 'A theory of cognitive aging (Timothy A. Salthouse, 2000) and was subsequently described as follows: '*The central hypothesis in the theory is that increased age in adulthood is associated with a decrease in the speed with which many processing operations can be executed and that this reduction in speed leads to impairments in cognitive functioning because of what are termed the limited time mechanism and the simultaneity mechanism* (T. A. Salthouse, 1996)*.'* When considering white matter pathways where the primary function is the transmission of information from one region of the brain to another, this theory is of integral importance. Some research groups have suggested that the processing speed theory does not exclude other theories of neurocognitive decline.
CHRUNCH (Compensation-Related Utilization of Neural Circuits Hypothesis)	This describes a difference a pattern of activation where older adults recruited the Dorsolateral Prefrontal Cortex (DLPFC) in a more bilateral manner than the younger adults to achieve the same scores when performing a working memory task (Reuter-Lorenz et al., 2001). This pattern of brain activation was coined 'Compensation-related utilization of neural circuits hypothesis or CRUNCH. (Reuter-Lorenz & Cappell, 2008) later explained that this *'age-related over activation'* or compensation may mask potential degradation of underlying neural substrates by sustaining cognitive performance in older adults.

HAROLD (Hemispheric Asymmetry Reduction in Older Adults)	The HAROLD hypothesis states that '*prefrontal activity during cognitive performances tends to be less lateralized in older adults than in younger adults'* (Cabeza, 2002). Developed from studies using fMRI measuring memory, inhibition and perceptual functions, Cabeza suggests that HAROLD could reflect a process of compensation *and* dedifferentiation. That is, specialization or specific brain regions regresses and a more generalized recruitment of brain regions take its place and the product is minimized loss of cognitive function.
PASA (Posterior – Anterior Shift in Aging)	Developed from predominantly PET and fMRI findings, the Posterior-Anterior Shift in Aging (PASA) hypothesis proposes that in older adults some posterior regions of the brain are recruited less, and some anterior (frontal) regions are recruited more compared to younger adults in order to complete certain tasks (Grady et al., 1994).

Appendix D Ethics and recruitment documents

Research Ethics Office

5.11 Franklin-Wilkins Building
(Waterloo Bridge Wing)
Stamford Street
London SE1 9NH
Tel 020 7848 4077/4070/4020
Email rec@kcl.ac.uk
www.kcl.ac.uk/research/ethics

KING'S College LONDON

Anoushka Leslie
Centre for Neuroimaging Sciences (PO89)
Institute of Psychiatry
King's College London
Denmark Hill
SE5 8AF

16 September 2011

Dear Anoushka

PNM/10/11-163 Mapping the relationship between the white matter and executive function across the adult lifespan.

Thank you for sending in the amendments requested to the above project. I am pleased to inform you that these meet the requirements of the PNM RESC and therefore that full approval is now granted.

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (http://www.kcl.ac.uk/college/policyzone/index.php?id=247).

For your information ethical approval is granted until **16 September 2014**. If you need approval beyond this point you will need to apply for an extension to approval at least two weeks prior to this explaining why the extension is needed, (please note however that a full re-application will not be necessary unless the protocol has changed). You should also note that if your approval is for one year, you will not be sent a reminder when it is due to lapse.

If you do not start the project within three months of this letter please contact the Research Ethics Office. Should you need to modify the project or request an extension to approval you will need approval for this and should follow the guidance relating to modifying approved applications: http://www.kcl.ac.uk/research/ethics/applicants/modifications.html

Any unforeseen ethical problems arising during the course of the project should be reported to the approving committee/panel. In the event of an untoward event or an adverse reaction a full report must be made to the Chairman of the approving committee/review panel within one week of the incident.

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance (http://www.kcl.ac.uk/research/ethics/contacts.html). We wish you every success with this work.

With best wishes

Yours sincerely

Jim Summers
Research Ethics Team Leader

c.c. Andy Simmons

www.kcl.ac.uk

Recruitment poster and permission letter

Dear Sir/Madam,

I would like to ask your permission to display a recruitment poster for participants to take part in a scientific research study we are conducting here at King's College London. The aim of the study is to build up an atlas of brain anatomy and cognitive ability of healthy adult volunteers over the age of 18 . We are particularly interested in how brain anatomy may change over the adult lifespan, and how this may relate to changes in cognitive ability with ageing.

Information that participants provide in the study will be fully anonymised. Participants are also free to withdraw from the study at any time, and they do not need to provide a reason for this. If participants express an interest in taking part, we will provide them with further information about the study (please see attached information sheet).

We feel that displaying this recruitment poster will be a good way to communicate this opportunity to people who may be interested in participating who are aged over the age of 65 (or between the ages of 30 and 65). Please see the attached poster for your reference.

We will be recruiting for this study over the next 12 months.

Please let me know if you would be happy to display the poster at your premises.

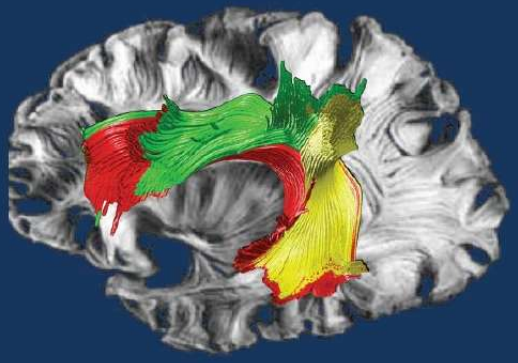
If you have any questions, then please do not hesitate to get in touch.

Kind regards,

Anoushka Leslie
e-mail: Anoushka.leslie@kcl.ac.uk
telephone:

RESEARCH ETHICS COMMITTEE REFERENCE NUMBER: PNM/10/11-163

Are you interested in taking part in a pioneering study to explore the geography of the brain and to map this to the way we **think**, **communicate**, use our **memories** and **make decisions**?



BRAIN EXPLORATION

We are looking for healthy volunteers over the age of 60, with no history of neurological or psychiatric disorder. £50 will be provided to compensate for the time taken for being involved in the study.

The study involves two scans, a small blood sample and some cognitive testing. £6 for lunch expenses will be provided during the second visit and all travel expenses will be reimbursed.

For more information, e-mail us brainatlas@kcl.ac.uk or call us on 07534 656 301

This study is being conducted at the Institute of Psychiatry, Denmark Hill.
As a volunteer, you are not obliged to respond to this poster,
if you decide to take part in the study,
you may withdraw at any time .

7.4 Recruitment e-mail

Dear all,

Study: Mapping the relationship between white matter and executive function across the adult lifespan.

This project contributes to the College's role in conducting research, and teaching research methods. You are under no obligation to reply to this email, however if you choose to, participation in this research is voluntary and you may withdraw at anytime.

The Centre for Neuroimaging Sciences in collaboration with the NIHR Biomedical Research Centre for Mental Health is building an atlas of the healthy developing human brain.

For this study, we are looking for healthy volunteers over the age of 18 with no history of neurological or psychiatric problems. Pictures of the brain will be collected using Magnetic Resonance Imaging (MRI) techniques. MRI is a safe method that can take pictures of the brain without the need for any radioactive substances. Here we are developing sophisticated scanning techniques that produce detailed maps which may be able to help us understand the ageing process better. We will also be conducting cognitive tests including those designed to measure general intelligence and something called Executive function. Executive function is used to describe the way the brain enables an individual to live an independent and purposeful life. These tests will be either pen and paper, or computer based. By looking at the anatomical pictures and linking them with different factors such as cognitive ability, age or genetic information we will get a better understanding of how the brain changes over time. With this information, the atlas will also facilitate further research regarding the analysis and interpretation of abnormalities occurring in neurological and psychiatric disorders. If you would like to take part, an information sheet is available with a detailed explanation of the study. You will be also asked to complete a more detailed screening questionnaire over the phone. Once you have been accepted onto the study, you will be invited to attend two appointments at the Centre for Neuroimaging Sciences in Denmark Hill.

What will you be asked to do?

First session:

1. We will ask you to complete some questionnaires.

2. Will take a small blood sample (no more than 20 millilitres / 4 teaspoons.

3. We will then ask you to take part in the first scan. There will be one functional task where you have to read and remember some letters during the scan.

Second session:

1. The first part will involve being interviewed, filling out some questionnaires and taking part in some computer and pen and paper-based tests.

2. The second part will involve another scan, where you can relax or sleep until the end of the exam.

How long will the study last?

If you wish to take part in all of the study, overall, this will take roughly one and a half days. We will schedule both sessions at a date convenient to you.

Session 1: You will need some time to complete the questionnaires. Then the first scan will take no more than 1 hour. The session overall will last no more than 2.5 hours.

Session 2: The second session will take less than a day to complete in the morning, you will spend approximately 3 hours completing the cognitive tests. (breaks provided). You will have a break for lunch and then in the afternoon, the scan will take approximately 1 hour.

A one-off fee of £20 will be paid when you complete your first scan. During the second visit we will provide £6 to cover lunch costs, and an additional sum of £30 to (scan and cognitive testing). We will also refund any travel expenses for you (we will need to see your travel tickets/receipts). This is to compensate you for your time, inconvenience and any travel expenses incurred. All participant information and data will be kept anonymous and held confidentially in line with the UK Data Protection Act 1998.

If you want get involved into this study please send an email to brain-atlas@kcl.ac.uk including your date of birth and gender. Please note that the MRI scanner consists of a powerful magnet, which may attract metallic objects. You can NOT have a scan if you have received metal injuries

to the eyes, had metallic or electronically, magnetically or mechanically activated objects (including clips, pacemakers) inserted to your body at an operation, have a fear of enclosed spaces, have facial tattoos, extensive dental work, or have received a shotgun or shrapnel injuries.

Many thanks

Anoushka Leslie

E-mail: Anoushka.leslie@kcl.ac.uk

brain-atlas@kcl.ac.uk

7.5 Information sheet

INFORMATION SHEET FOR PARTICIPANTS

REC Reference Number: **PNM/10/11-163 Mapping the relationship between the white matter and executive function across the adult lifespan.**

Title of study: Mapping the relationship between white matter and executive function across the adult lifespan.

We would like to invite you to participate in this original postgraduate research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

Aims of the research and possible benefits

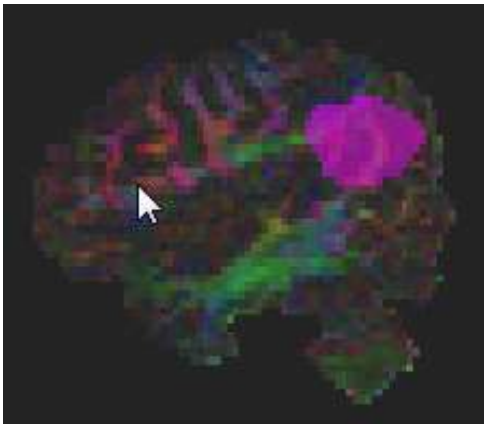
A lot of information is already available showing how cognitive performance changes with age. (cognitive performance means the ability of an individual to perceive and process information; remember and recall information; maintain attention; problem solve; reason or think in abstract ways and to plan). There is also quite a lot of research looking at surface anatomy of the brain and how this changes with age. Recently, new techniques have been developed to explore the deeper white matter structures within the brain, but there has not been as much research looking into how these structures change with age, and even less that maps such changes to cognitive performance. In this study we aim to build up an atlas of the white matter anatomy of the brain of healthy adult volunteers over the age of 18. We will then map genetic information and cognitive performance information of individuals to their brain anatomy.

The way will gather this information is as follows:

Imaging techniques:

Pictures of the brain will be collected using Magnetic Resonance Imaging techniques. These pictures are extremely valuable to us because here at the Centre for Neuroimaging Sciences, we have special protocols and machines that can take pictures of the brain which cannot be obtained normally in other centres. With these pictures, we hope to be able to understand more about the structure and the function of the brain. By linking information from the images to other factors such as age, we will get a better understanding of how the brain develops throughout the adult lifespan.

Example of images showing some neuronal pathways within the brain [Arcuate fasciculus]



Cognitive tests:

We will also be conducting cognitive tests including those designed to measure general intelligence, memory function and something called Executive function. Executive function is used to describe the way the brain enables an individual to live an independent and purposeful life. It enables people to know what they need to do to look after themselves, and plan and prioritise activities to lead them through their life in a way that is meaningful, productive and beneficial way. For example, Executive function includes simple everyday activities like shopping for weekly groceries, to more complex ones like being able to plan a holiday or long journey.

DNA and RNA analysis

We will also be collecting a small blood sample (20 millilitres / 4 teaspoons) to gather genetic information and link this to brain anatomy. From that blood sample we will extract DNA and RNA information to examine whether or not there are genetic influences related to anatomy and / or cognitive performance changes with age. The blood sample will be taken by a trained phlebotomist or medical professional. There will be a slight risk of bruising as a result of the blood sample being taken.

By providing a detailed picture of how the anatomy of the brain, genetic information and cognitive ability changes with age in normal healthy subjects, we will be providing a baseline from which anomalies in brain anatomy and function in different patient groups can be explored.

Who have we asked to participate?

For this study, we are looking for healthy volunteers over the age of 18

Who do we have to exclude?

We will not be able to scan anyone who has any history of neurological disorders or of mental illness.

Please note that the MRI scanner consists of a powerful magnet, which may attract metallic objects. You can NOT have a scan if you have received metal injuries to the eye, had metallic or electronically, magnetically or mechanically activated objects (including clips, pacemakers) inserted to your body at an operation, have a fear of enclosed spaces, weigh more than

220 lbs (100kgs), has facial tattoos, extensive dental work, or has received any shrapnel injuries.

When and where will the study take place?

The study is made up of two sessions. These sessions will normally be conducted Mon-Fri during working hours (between the hours of 9.00am – 5.00pm). The study will take place at:

Centre for Neuroimaging Sciences,

Box 089, Institute of Psychiatry,

De Crespigny Park, London SE5 8AF, UK.

What will you be asked to do?

Screening call: We will call you and ask you to answer some MRI safety and study screening questions before we schedule the scans. This is to ensure that it is safe for you to take the MRI, and that you fulfil the specific criteria for this research study. If you do not meet the eligibility criteria at this stage, we will destroy the data collected during the call. All information provided during the call will treated confidentially.

First session:

i. We will ask you to complete some questionnaires.
ii. Will take a small blood sample.
iii. We will then ask you to take part in the first scan. There will be one functional task where you have to read and remember some letters during the scan.

Second session:

- The first part will involve being interviewed, filling out some questionnaires and taking part in some computer and pen and paper based tests.
- The second part will involve another scan, where you can relax or sleep until the end of the exam.

How long will the study last?

If you wish to take part in all of the study this will take roughly one and a half days overall.

We will schedule both sessions at a date convenient to you.

The first scan will take no more than 1 hour. The session overall will last no more than 2.5 hours.

The second session will take less than a day to complete (no more than 5.5 hours in total). In the morning, you will spend approximately 3 hours completing the cognitive tests with breaks provided as required. You will have a break for lunch and then in the afternoon, the second scan will take approximately 1 hour.

What are the risks?

These can be a minor risk of some bruising when the blood sample is taken.

MRI scanners can be very loud but we will provide ear protectors to reduce the sound. When taking the scan, you will be asked to lie down in the scanner for an hour without moving which could cause some discomfort.

The neuropsychological tests will mainly involve being interviewed, filling out questionnaires, using a pen and paper or conducting tests using a computer. We will have breaks during the testing and you can ask to take a break at any point. If you find any of the questions awkward, or wish to stop any of the tests, we will stop the test and only continue when you give us permission.

Are there any benefits in being involved in the study?

Participants will be reimbursed travel expenses and paid £20 at the end of the first session and a further £30 at the end of the second session. On request, participants will be sent a copy of the final project report.

How will we maintain your privacy and confidentiality?

Once you have agreed to take part in the study, any personal information (such as your name, date of birth and contact details) will be encrypted and stored securely. All your records will be identified using a barcode number rather than your name. Only the study team or MindSearch will have access to your information. All information, including research data and consent form and administrative records will be kept securely. Any of your data used in the study will be anonymised which this means that there will be no way that information can be used in a way to identify you in the report.

If any information we gain from the study may warrant further investigation, we will contact your GP. Check wording..

Who is organising and funding the research?

Dr Andy Simmons is the overall organiser of this project. The principal investigators are Dr Flavio Del Aqua and Anoushka Leslie. The study is being funded by the Biomedical Research Centre for Mental Health.

What if I want to withdraw from the study?

Participation in this research is voluntary. It is up to you to decide whether to take part or not. If you decide to take part you are still free to withdraw at any time and without giving a reason.

In addition to withdrawing yourself from the study, you may also withdraw any data/information you have already provided up until it is transcribed for use in the final report or a paper has been submitted for publication.

What if I have questions about the study?

If you have any further questions about this study, please e-mail brain-atlas@kcl.ac.uk. If this study has harmed you in any way you can contact King's College London using the details below for further advice and information:

NAME AND CONTACT DETAILS OF RESEARCHERS

Researcher Supervisor:

Dr Andy Simmons

e-mail: andy.simmons@kcl.ac.uk

Telephone: 020 3228 3060

If you have any general queries about the study, please contact either Anoushka Leslie or Flavio Dell' Acqua.

Anoushka Leslie

e-mail: anoushka.leslie@kcl.ac.uk

Telephone: to be confirmed

Flavio Dell Acqua

e-mail: flavio.dellacqua@kcl.ac.uk

Telephone: to be confirmed

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: Mapping the relationship between white matter and executive function across the adult lifespan.

This study is affiliated with the programme:

King's College Research Ethics Committee Ref:

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

1. I understand that if I decide at any time during the research that I no longer wish to participate in this project, I can notify the researchers involved and withdraw from it immediately without giving any reason. Furthermore, I understand that I will be able to withdraw my data up to March 2014.

2. I give my consent for my blood to be genotyped for this study.

3. I understand that I will not receive any results about my own genotype.

4. I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the Data Protection Act 1998.

    1. The information I have submitted will be published as a report and I can be sent a copy. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.

    2. I agree that the research team may use my data for future research and understand that any such use of identifiable data would be reviewed and approved by a research ethics committee. (In such cases, as with this project, data would not be identifiable in any report).

    3. I agree that my GP may be contacted if any unexpected results are found in relation to my health.

I would/would not like to receive information on the outcome of the study (delete whichever does not apply).

Participant's Statement:

I _____

agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

Signed **Date**

Investigator's Statement:

I _____

Confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant.

Signed **Date**

Institute of Psychiatry

at The Maudsley

Screening template

KING'S College LONDON
University of London

Outcome of screening: Included / Excluded

SCREENING QUESTIONNAIRE

Study: PNM/10/11-163 Mapping the relationship between the white matter and executive function across the adult lifespan.

Date form completed		Researcher	

Contact Details:

Name:

Address:

Daytime telephone number:

Email address:

Socio-Demographics:

Date of birth

Age:

Right Handed? YES/NO

Occupation:

First language English?

Are you registered with a GP in the UK? YES/NO

Please supply address:

General Inclusion and Exclusion Criteria: (please circle appropriate response)

Height:

Weight:

Do you currently smoke cigarettes/use any nicotine-containing products? /? YES/NO

If yes how many a day? ……*(<5 /day)*

Do you or have you ever currently take recreational drugs (e.g. cannabis, ecstasy, cocaine)? ? YES/NO

If yes, what and how often?

Do you currently drink alcohol YES/NO

Medical History:

Have you ever had any psychiatric illness or depression, now or in the past? YES/NO

If yes, details *(e.g. suicide attempt/panic attacks/psychotic episodes)*

Are you currently taking any medication, vitamins or herbal supplements? YES/NO

If yes, details *(name and reason for taking*

Have you ever had a head injury which resulted in a loss of consciousness? YES/NO

If yes, details

Do you, or have you ever, suffered from epilepsy or seizures, *(more than one febrile convulsion)*? YES/NO

Have you ever been diagnosed with a medical condition by a Doctor? YES/NO

If so, details/name of condition

History of clinically significant disease affecting the blood, kidneys, endocrine system, lungs, stomach or gastrointestinal system, heart, liver, brain or allergies? YES/NO

Have you recently taken part in a scanning study? *(>3 months)*? YES/NO

Is there any chance that you may be pregnant? YES/NO

Do you use the coil as contraception? YES/NO

Scanning Questions:

Do you have a fear of needles/blood? YES/NO

Do you have a pacemaker or artificial heart valve? YES/NO

Do you have a hydrocephalus shunt? YES/NO

If so, is it a programmable shunt? / YES/NO

Have you had any operations on your heart, head, ears or spine? YES/NO

If yes, details

Have you had any surgery to you head or body ever/within the last 2 months *(abdominal surgery)?* YES/NO

If yes, details

Do you have any joint replacements or metal implants? YES/NO

If yes, details

Do you have any other metal inside your body? YES/NO

If yes, details

Have you EVER had metal in your eyes or worked with metal at high speed, e.g. in a machine shop? YES/NO

Do you have any shrapnel from a war injury? YES/NO

Do you wear a false limb, caliper or brace? YES/NO

Do you have dentures, a dental plate or a hearing aid? YES/NO

Do you have any ear implants, e.g. cochlear? YES/NO

Do you have problems lying still for a length of time for any reason? YES/NO

Do you suffer from claustrophobia? YES/NO

Have you any tattoos or piercings? YES/NO

If so where

Follow up actions (for researcher): **Follow-up by (date)**……

Surgery notes: (Procedure description, Date, Hospital, Patient reference number)

Follow up notes:	
Date	**Notes**

Appendix E Neuropsychological Assessment Instructions

Cambridge Brain Sciences Executive Function Task

These instructions were taken from the Cambridge Brain Sciences closed URL online task battery.

7.6.1 Spatial span

In this test you have to try to remember a sequence of flashing boxes that will appear on the screen one after the other. When you hear the beep click on the boxes in the same order in which they flashed. If you are correct, the next problem will have one more box in the sequence. If you make a mistake then the next sequence of boxes will be one shorter. After three errors, the test will end.

7.6.2 Paired associates

In this task you must remember which object appeared in which location. A set of boxes will appear on the screen. The boxes will open one after the other to reveal the object inside. You must remember which object appeared in which box. Subsequently, the objects will be displayed one after the other in the centre of the screen. When this happens, you must click on the box that contained that object.

7.6.3 Colour-word remapping

This test will stretch your brain's attentional abilities to the limit. Three words will appear on the screen, one at the top, and two at the bottom. Click on the word at the bottom of the screen that correctly describes the colour of the ink that the word at the top of the screen is written in. For example, if the word at the top of the screen is written in red ink, you should answer by clicking the word RED at the bottom of the screen. Solve as many problems as you can in 90 seconds

7.6.4 Feature match

This test measures your brain's ability to perceive and process complex visual stimuli. Two boxes will appear on the screen, each containing a complex array of abstract shapes. Are the two boxes identical or are they different? Click Match or Mismatch to indicate your answer.

If you get it correct, the next problem will be more difficult. If you get it wrong, the next problem will be easier. Solve as many problems as you can in 90 seconds.

7.6.5 Hampshire tree

This test measures your brain's perceptual acuity. Two panels will appear, one containing two overlapping shapes and the other containing just one shape. Is the single shape identical to one of the overlapping shapes or is it subtly different? Click Match or Mismatch to indicate your answer. If you get it correct, the next problem will be more difficult. If you get it wrong, the next problem will be easier. Solve as many problems as you can in 90 seconds

7.6.6 Spatial search

This test measures your ability to plan and organise the contents of your memory. Some boxes will appear on the screen. A token will be hidden in one of the boxes. Your task is to search through the boxes, by clicking on them, until you find a token. Once you have found a token you have to try and remember where this was hidden, as a token will never be hidden in the same box again. You have to continue to search and collect all of the tokens, until one has been found in every box. When you are searching, if you look in the same box twice before you find a token, then you will lose a life.

7.7 Edinburgh handedness questionnaire

Please indicate your preferences in the use of hands in the following activities by putting + in the appropriate column. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, put ++. If in any case you are really indifferent put + in both columns. Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets. Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

Question	Left	Right
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without a fork – e.g. cutting a loaf of bread)		
7. Spoon		
8. Broom (Upper hand)		
9. Striking match (Match)		
10. Opening box (lid)		
a) Which foot do you prefer to kick with?		
b) Which eye do you use when using only one?		

For researcher completion:

L.Q		DECILE

7.8 Mini mental state exam (MMSE

Orientation – 10 points

Ask the following questions:

1. What is today's date?

2. What is the month?

3. What is the year?

4. What day of the week is it today?

5. What season is it?

6. What is the name of this clinic (place)?

7. What floor are we on?

8. What city are we in?

9. What county are we in?

10. What country are we in?

Orientation subtotal = /10

Immediate Recall – 3 points

Ask the subject if you may test his/her memory. Then say "ball", "flag", "tree" clearly and slowly, about 1 second for each. After you have said all 3 words, ask him/her to repeat them - the ***first*** repetition determines the score (0-3):

11. BALL

12. FLAG

13. TREE **Recall subtotal = /3**

Attention – 5 points

NB PERFORM SERIAL 7S **OR** 'WORLD' BACKWARDS **BUT NOT BOTH**!

A) Ask the subject to begin with 100 and count backwards by 7. Stop after 5 subtractions. Score the correct subtractions.

14. "93"

15. "86"

16. "79"

17. "72"

18. "65"

~~B) Ask the subject to spell the word "WORLD" backwards. The score is the number of letters in correct position. For example, "DLROW" is 5, "DLORW" is 3, "LROWD" is 0.~~

~~"D"~~

~~"L"~~

~~"R"~~

~~"O"~~

~~"W"~~ **"DLROW" or Serial 7s subtotal = /5**

Delayed Verbal Recall – 3 points

Ask the subject to recall the 3 words you previously asked him/her to remember.

19. BALL?

20. FLAG?

21. TREE?

Delayed verbal recall subtotal = /3

Naming –2 points

Show the subject a wrist watch and ask him/her what it is. Repeat for pencil.

22. WATCH

23. PENCIL

Repetition – 1 point

Ask the subject to repeat the following :"No ifs, ands, or buts"

25. REPETITION

3-Stage command - 3 points

Give the subject a plain piece of paper and say, "Take the paper in your hand, fold it in half, and put it on the floor."

25. TAKES

26. FOLDS

27. PUTS

Reading – 1 point

Hold up the card reading, "Close your eyes", so the subject can see it clearly. Ask him/her to read it and do what it says. Score correctly only if the subject actually closes his/her eyes.

28. CLOSES EYES

Writing 1 point

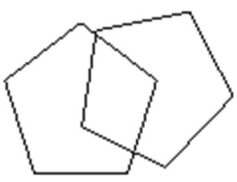
Give subject a piece of paper and ask him/her to write a sentence. It is to be written spontaneously. It must contain a subject and verb and be sensible. Correct grammar and punctuation are not necessary.

29. SENTENCE

Language subtotal = /8

Copying – 1 point

Give subject a piece of paper and ask him/he to copy a design of two intersecting shapes. One point is awarded for correctly copying it. All angles on both Figures must be present, and the Figures must have one overlapping angle.

Example: 

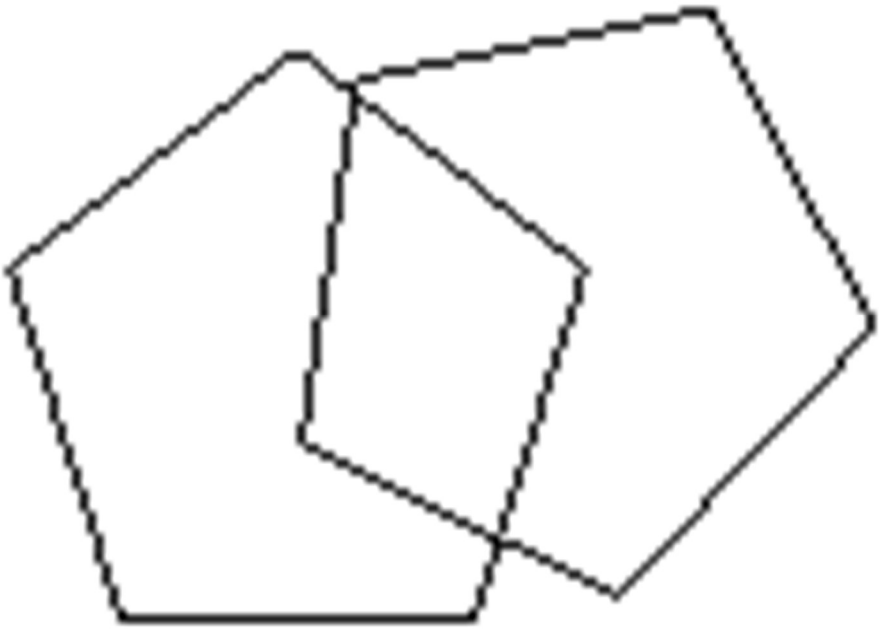
30. PENTAGONS

Pentagon subtotal = /1

TOTAL MMSE = /30

(MMSE maximum score = 30)

The examination has been validated in a number of populations. Scores of 25-30 out of 30 are considered normal, 18-24 indicate mild to moderate impairment, and scores of 17 or less indicate severe impairment.



CLOSE YOUR EYES

7.9 Ravens progressive matrices (RPM)

Instructions provided in booklets from:

https://www.pearsonclinical.co.uk/Psychology/AdultCognitionNeuropsychologyandLanguage/AdultGeneralAbilities/Ravens-Progressive-Matrices/Ravens-Progressive-Matrices.aspx

7.10 BRCATLAS full list of imaging and behavioural measures

7.10.1 Neuropsychological assessments

#	Test name	Purpose of test
1	**Mini Mental State Examination**	To screen or mild cognitive impairment or dementia for participants over the age of 60.
2	**Eysenck Personality Questionnaire**	To establish participants score on the following scales: 1. Extraversion/Introversion 2. Neuroticism 3. Psychoticism /Socialisation
3	**Behavioural impulsivity scale 11**	30 questions to measure general impulsivity.
4	**Edinburgh handedness inventory**	Establish handedness and contribute to information associated with brain lateralisation.
5	**Reaction time test**	Reaction time. Motor -reaction time is known to reduce with age. Reaction time data will be compared with decision times for various time-bound tasks.
6	**Peg board test** In collaboration with Dr Catani	Attention and motor lateralisation. May potentially be associated with short U-shaped fibres linking motor and sensory areas in the brain.
7	**Line bisection** In collaboration with Dr M Thiebaut de Schotten	Can screen for unilateral spatial neglect; Can highlight attentional or motor biases.
8	**Mental line bisection** In collaboration with Dr M Thiebaut de	Thought to measure similar functions to Line bisection: Spatial neglect (as above) may also impact the way we use the mental number line when bisecting it. Unusual lateralisation of line bisection may indicate prefrontal damage and spatial working memory deficits.
9	**Ravens' progressive matrices**	Measurement of the 'eductive' general intelligence.
10	**National adult reading test**	Intelligence

11	**Posner paradigm** In collaboration with Dr Thiebaut de Schotten	Spatial attention – may be associated with the superior longitudinal fasciculus (SLF)
12	**Change Detection Task** In collaboration with Dr Mario Parra	This test has shown sensitivity with familial Alzheimer's Disease gene carriers, which in turn may indicate sensitivity to aging populations.
	Cambridge Brain Sciences Tests battery	
13	Spatial Span	Working memory
14	Paired associate	Paired associate learning
15	Feature match	Visual attention
16	Spatial planning	Planning
17	Spatial search	Reasoning and working memory
18	Color-word remapping	Interference control (attention)

7.10.2 Neuroimaging measures

Gated DWI image (32 directions) for Diffusion Tensor Imaging

Gated DWI image (60 directions) for Spherical Deconvolution

Magnetisation Prepared Rapid Acquisition Gradient Echo (MPRAGE) structural scan

Fluid Attenuated Inversion Recovery (FLAIR) MRI scan

Driven Equilibrium Single Pulse Observation of T_1 or T_2 (DESPOT)

fMRI N-back paradigm

Appendix F Dissection Protocols

All dissection protocols described in this thesis are based upon those practiced by the expert operators within the Natbrainlab. Detailed descriptions of common artefacts occurring using these protocols are either based upon observations made by members of the natbrainlab or by the main operator AL.

7.11 Cingulum

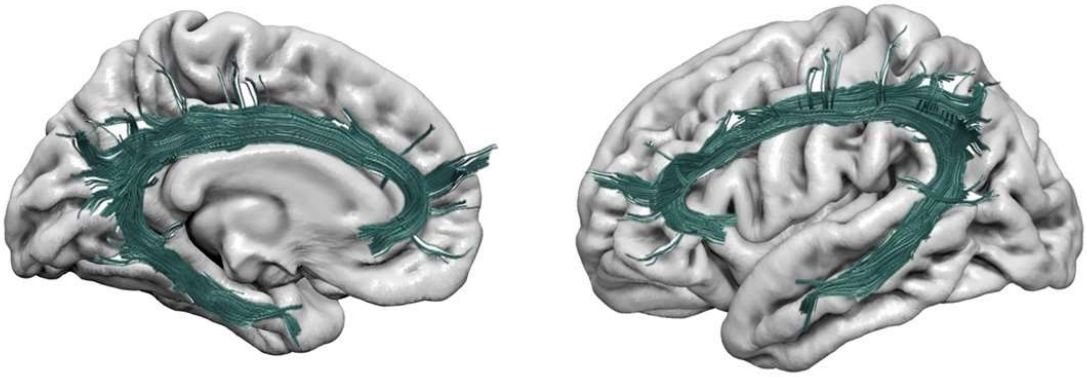


Figure 84 SD reconstruction of the cingulum from lateral and medial aspects

This thesis has used two different approaches to dissect the cingulum. A single ANDROI and a double ANDROI approach.

7.11.1 Single ANDROI dissection protocol

7.11.1.1 Regions of interest (1 ANDROI)

Table 25 List of Regions of Interest (ROI) using 1 ANDROI cingulum protocol

	Region of Interest	Description
1	CING ANDROI Left	A single ROI drawn on the axial slices covering the entire cingulum.
2	NR Sag1	Cuts out any fibres crossing over between hemispheres
3	NR Cor1	Removes artefacts travelling in an anterior-posterior direction
4	NR SLFI	Removes sections of the SLFI dorsal to the cingulum

7.11.2 Step by step instructions (1 ANDROI)

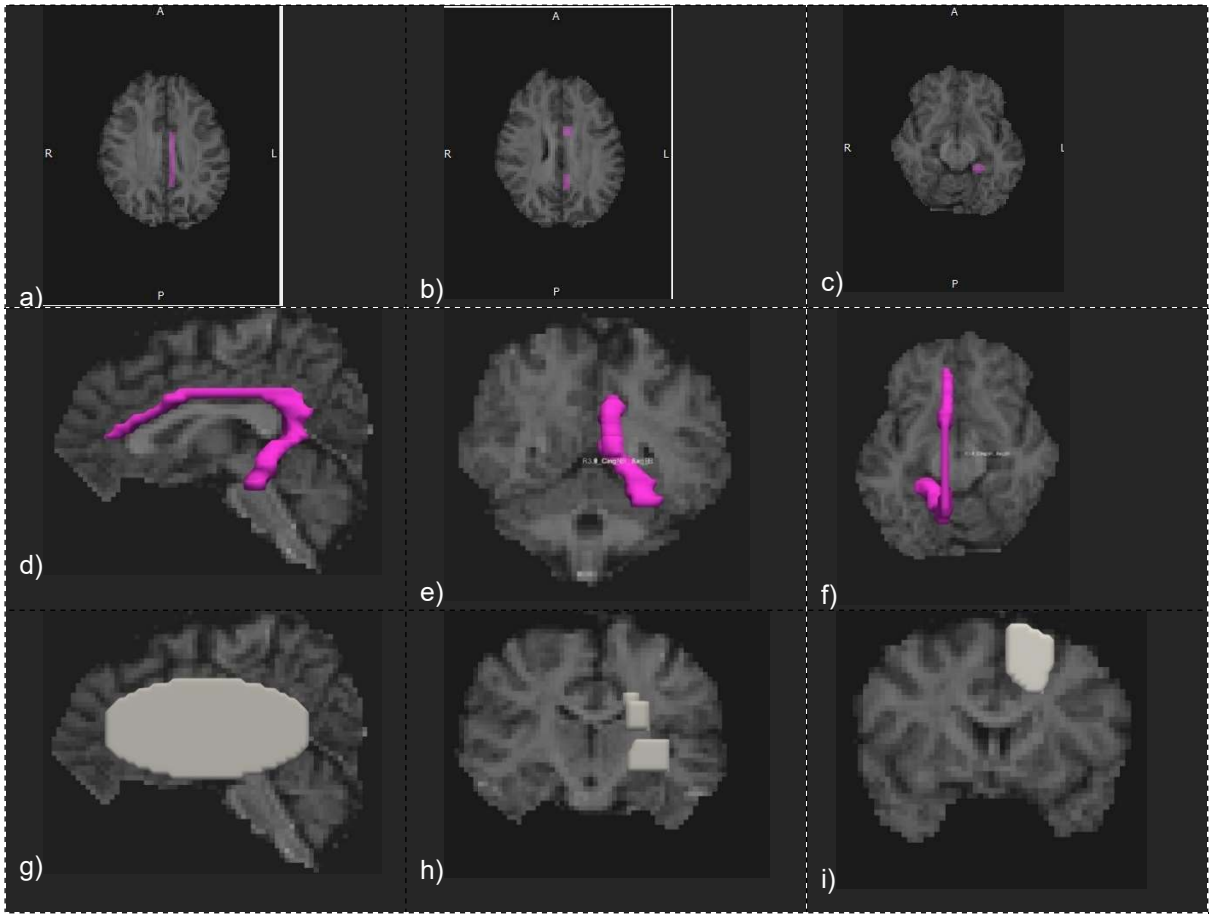


Figure 85 cingulum 1ANDROI dissection protocol

1. **Draw Axial ANDROI.** Use the axial panel and go to the most dorsal slice. Scroll down until a thin band travelling anterior to posterior over the corpus callosum becomes visible (Fig. 85a). Draw the ROI around this thin band. Move to the next slice down and repeat. Continue until the thin band is separated and draw the ROI around the anterior and posterior segments that are anterior and posterior to the crux of the corpus callosum (Fig. 85b). Below the corpus callosum only the posterior segment of the cingulum will now be visible. Draw around it. It will gradually appear more laterally as it moves into the temporal lobe (Fig. 85c). When completed the ROI will be shaped in the form of the cingulum (Fig. 85d-f). Be careful not to place the ROI onto any corpus callosum fibres. To check, look at the sagittal plane, midline to see if there is any overlap between cingulum ANDROI and corpus callosum fibres.
2. **Draw sagittal midline NOTROI:** Using the sagittal plane, draw a large oval NOTROI to cover all potential crossing fibres between hemispheres (Fig. 85g).
3. **Draw coronal NOT ROIs:** As needed, if there are any artefact fibres from the cingulum, a NOTROI placed at different points on the Coronal plane will remove them (Fig. 85h).

4. **Draw coronal NOTROI for SLF**: In the sagittal plane, locate the anterior commissure. Align the coronal plane to this point. In the coronal plane draw a NOTROI around the white matter *dorsal* to the cingulum (i.e. the SLFI) (Fig. 85g).
5. **Create Tract and Toggle:** Create tract from CING AND ROI. Toggle with appropriate NOT ROIs and save.

7.11.3 2 Double ANDROI dissection protocol

7.11.3.1 Regions of interest (2 ANDROI)

Table 26 List of Regions of Interest (ROI) using 2 ANDROI cingulum protocol

	Region of Interest	Description
1	CING_ANDROI_1_Left	One ROI positioned in two separate places, first on a coronal plan and second on an axial slice.
2	CING_ANDROI_2_Left	Another ROI positioned in two separate places, first on a coronal plan and second on an axial slice.
3	NR_Cor1	Removes artefacts travelling in an anterior-posterior direction
4	NR_Sag1	Cuts out any fibres crossing over between hemispheres.
5	NR_Ax1	Removes sections of the SLFI hooking over the anterior cingulum

7.11.3.2 Step by step instructions (2 ANDROI)

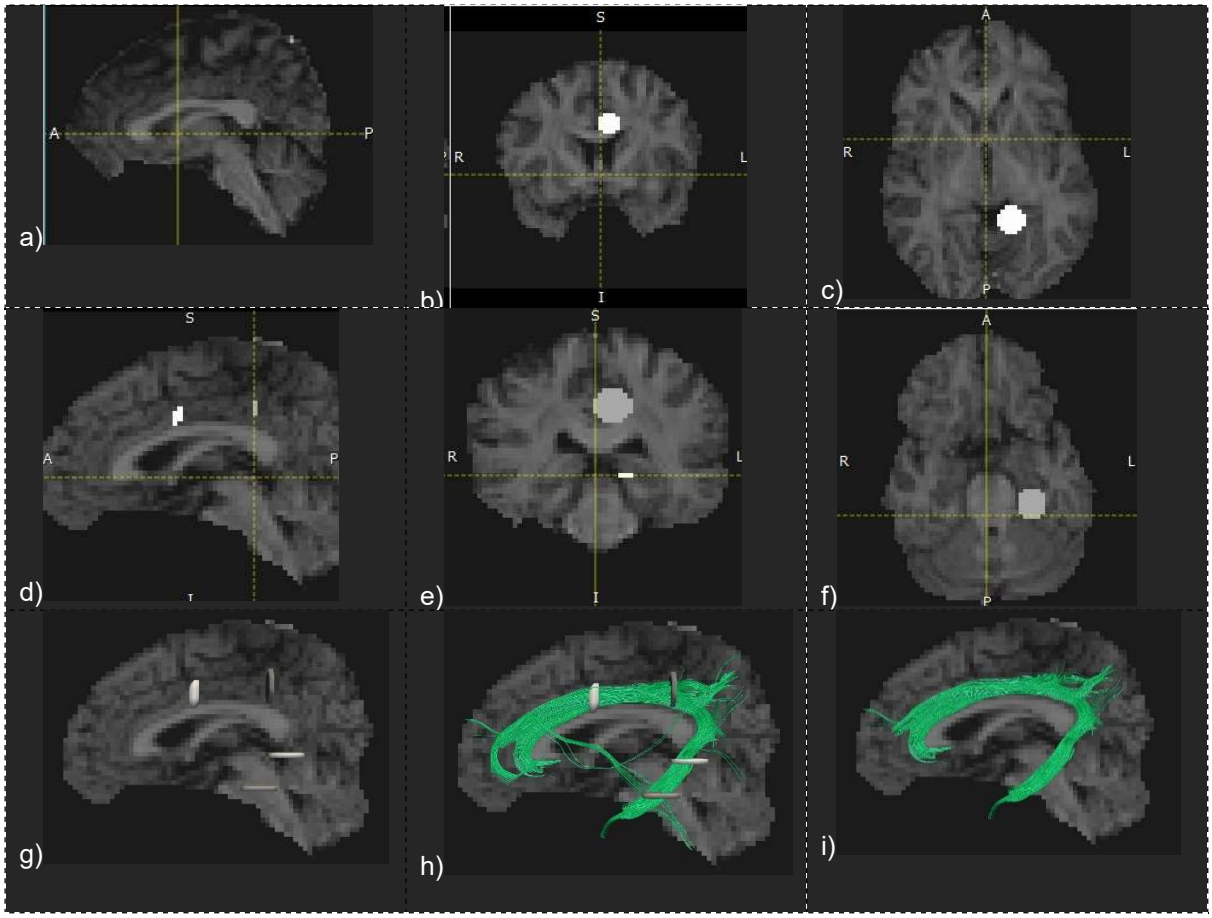


Figure 86 cingulum 2ANDROI dissection protocol

This dissection protocol uses 2 ROIs ‘interleaved’ to ensure the sharp curve of the caudal section of the cingulum is captured fully.

1. **For ANDROI1:** Go to the sagittal midline and locate the anterior commissure (Fig. 86a). Place the coronal slice at its most anterior limit, place the coronal slice. On this slice, at the position of the cingulum, provide a circular ROI (Fig. 86b). Repeat one slice posterior. Still at the sagittal midline on the axial plane, place the axial slice at the Anterior Commissure (Fig. 86a, b) and place a second circle ROI (same ROI) on the axial plane at the position of the cingulum (Fig. 86c).
2. **For ANDROI2:** Return to the sagittal midline and move the coronal slice back until it is positioned between the posterior limit of the midbrain and the splenium of the corpus callosum (Fig. 86d) At this point examine the coronal slice and place a second round ROI over the cingulum (Fig. 86e). Move the axial slice ventrally for 6 slices until you can see the temporal trunk of the cingulum bundle to the left of the pons/midbrain. At this point, place a second circle (same ROI) around the para-hippocampal section of the cingulum (Fig. 86e).
3. Create track from ANDROI1 and toggle with ANDROI2.
4. For the 2ROI approach there tends to be less artefacts, but for those that exist remove as per the 1ROI instructions.

7.11.4 Common artefacts

Coronal NOTROI: The most common artefacts for the cingulum are fibres that are connected to neighbouring tracts such as the SLFI or IFOF or ILF. Most artefacts can be removed using coronal NOTROIs (Fig. 87, 88). From these it is clear that the double ANDROI approach generates less artefacts.

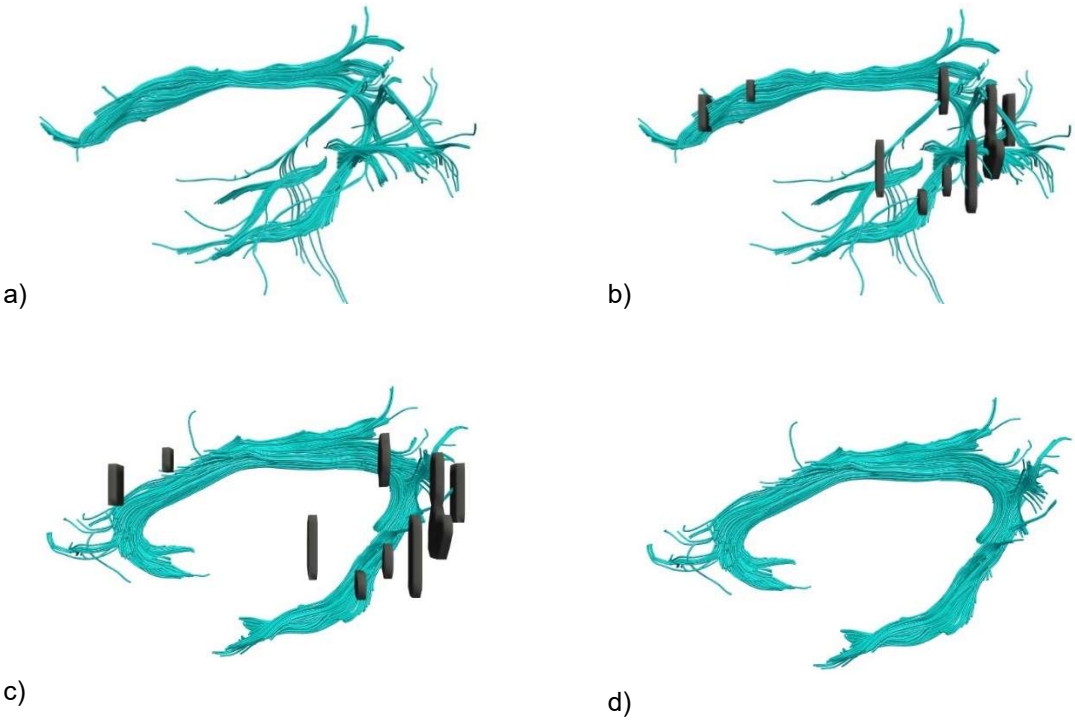


Figure 87 Cingulum from 1ANDROI protocol (blue) with artefact fibres removed by NOTROIs

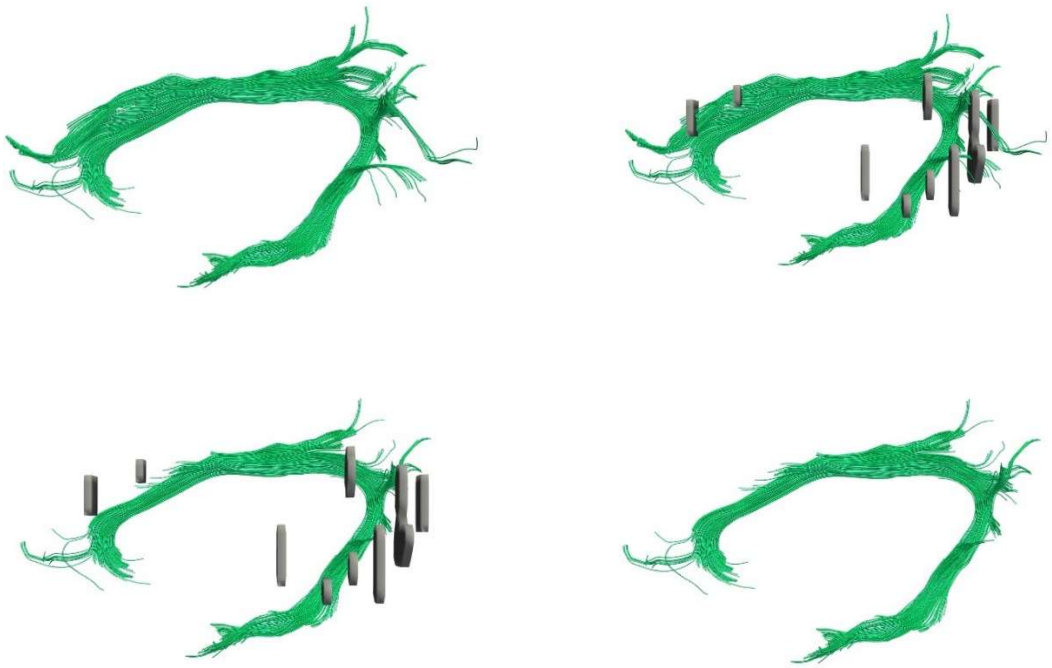


Figure 88 Cingulum from 2ANDROI protocol (green) with artefact fibres by NOTROIs

Sagittal NOTROI: Placed on the sagittal midline over the corpus callosum this NOTROI can remove any spurious fibres crossing to the alternate hemisphere.

Axial NOTROI: Anterior 'hook': A 'hook' like artefact, possibly due to proximal fibres from the SLFI can be removed by an axial NOTROI (Fig. 89 g - i).

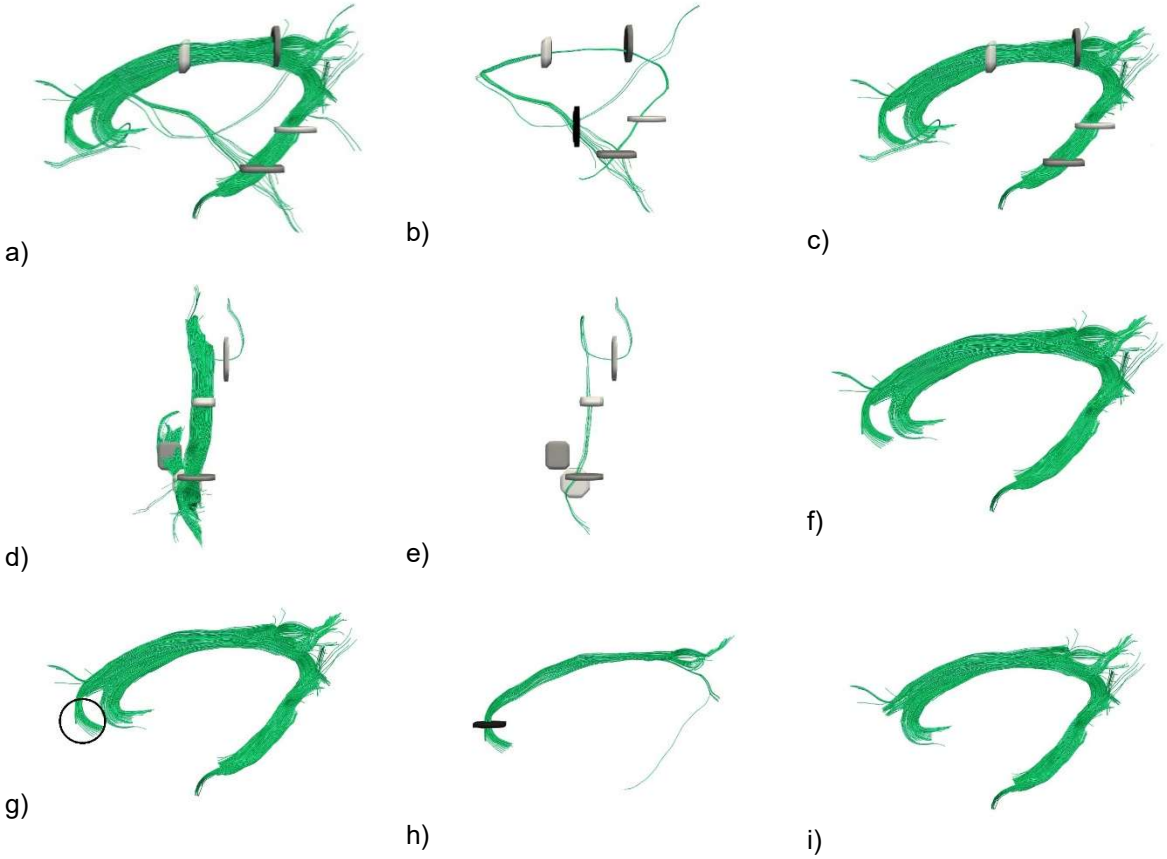


Figure 89 Further use of NOTROIs to remove artefacts from the cingulum

7.12 Corpus Callosum

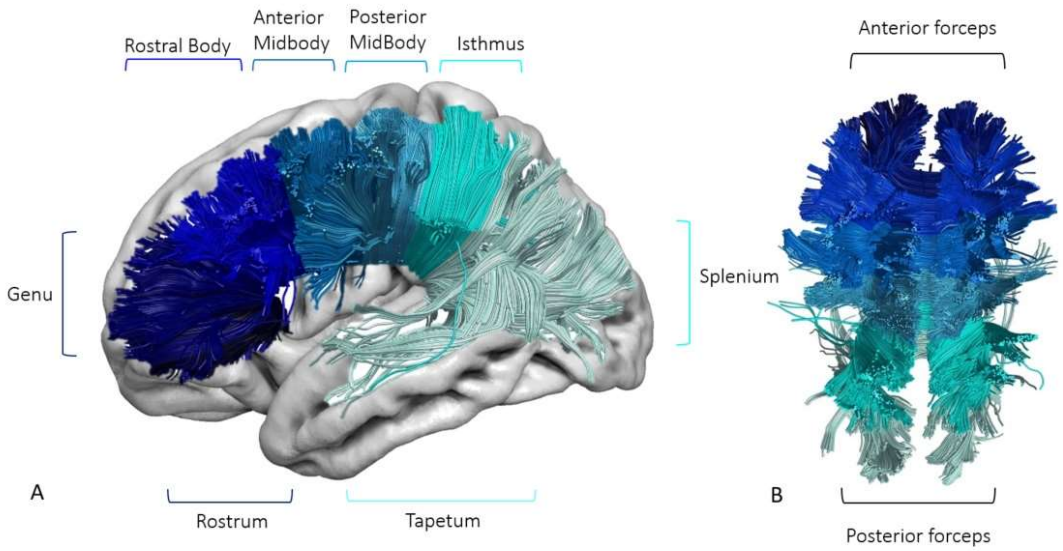


Figure 89 Five segments of the corpus callosum, lateral and dorsal views

7.12.1 Regions of interest

Table 27 List of Regions of Interest (ROI) for corpus callosum

	Region of interest	Description
1	Rostrum	Caudal/orbital prefrontal, inferior premotor
2	Genu	Prefrontal
3	Rostral Body	Premotor, supplementary motor
4	Anterior midbody	Motor
5	Posterior midbody	Somaesthetic, posterior parietal
6	Isthmus	Superior temporal, posterior parietal
7	Splenium	Occipital, inferior temporal
8NR	Cortico-spinal NOT ROI	Not ROI removing artefact fibres from neighbouring projection tracts
9NR	ILF (Coronal) NOT ROI	NOTROI removing artefact fibres from neighbouring ILF

7.12.2 Step by step instructions

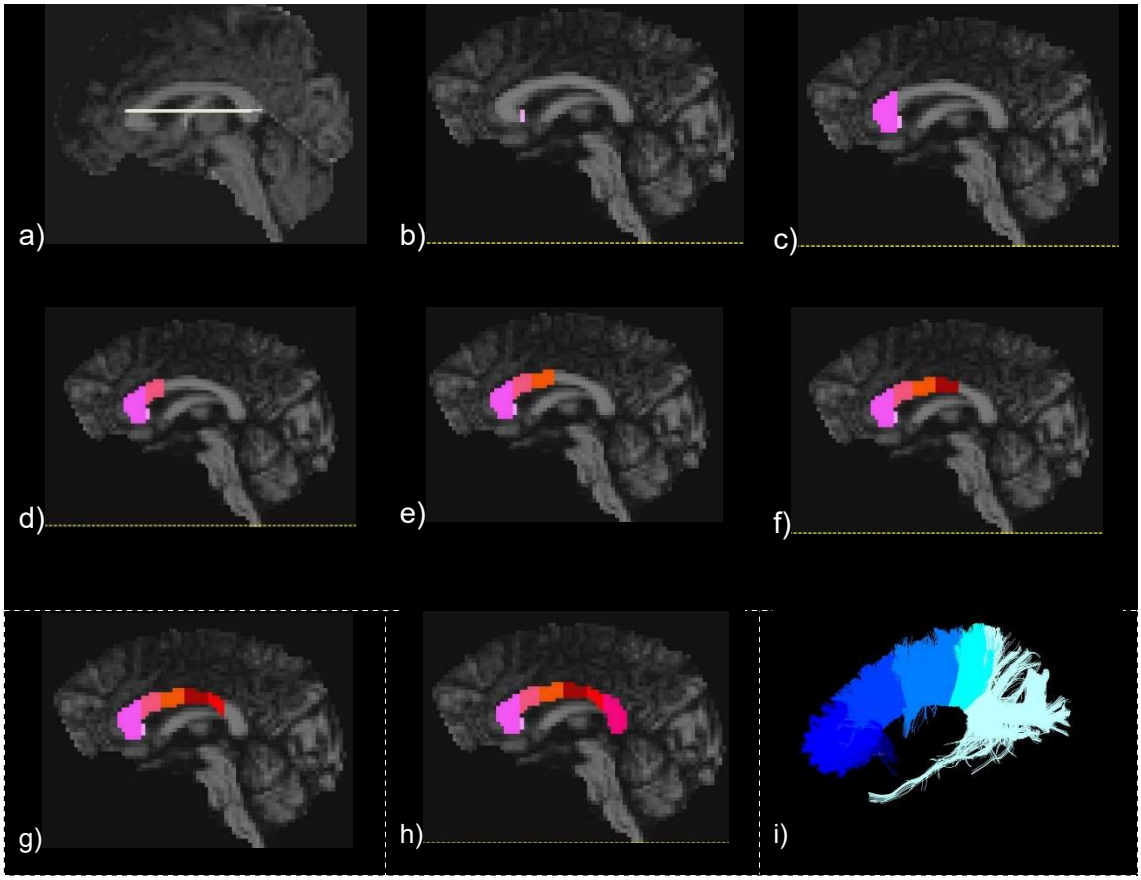


Figure 90 corpus callosum segmentation protocol

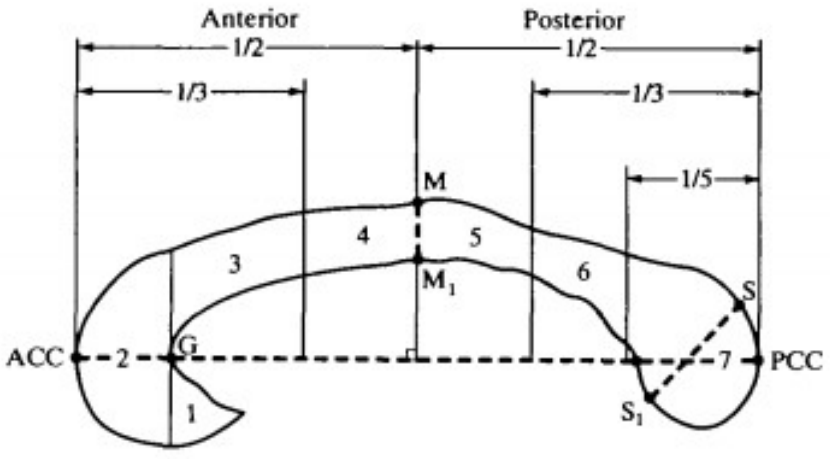


Figure 91 Segmentation, (Witelson 1989)

7.12.3 Step by step instructions

1. **Orientation.** This dissection protocol is based on one described by (Witelson, 1989a) (see Fig 91). On the mid-sagittal slice identify the most anterior (ACC) and posterior (PCC) point of the corpus callosum and draw a temporary ROI line between the two (Fig. 90a). Count the total number of voxels between ACC-PCC and input into spreadsheet.

2. Set up the spreadsheet to automatically calculate a half, third, fifth and sixth of the total number of voxels from ACC to PCC.

3. **Rostral (CC1) and Genu (CC2) ANDROIs:** Draw a vertical line at 'G', the convexity of the genu (Fig. 90b). This line will divide the Genu from the Rostrum (Fig. 90c) and the Rostralbody Fig. 90d). [In cases where voxel boundary is indistinct at 'G', use the calculation of a sixth of the total length from the ACC and round up or down using guidelines below].

1. **Rostral Body (CC3):** Count 1/3 back from ACC and draw a vertical line dividing the Rostral Body and the Anterior Midbody (Fig. 90de).

2. **Anterior Midbody (CC4):** Count 1/2 back from ACC and draw a vertical line dividing the anterior midbody and the posterior midbody (Fig. 90f).

3. **Posterior Midbody (CC5):** From the most posterior point of the corpus callosum (PCC), count 1/3 forward to draw a vertical line to divide the body posterior midbody and the Isthmus (Fig. 90g)

4. **Isthmus (CC6) and Splenium (CC7):** From the PCC count 1/5 to draw a line to separate the isthmus (6) and the splenium (7) (Fig. 90h).

5. Create tracks for each ROI.

Guidelines for rounding voxel counts up and down:

When using the spreadsheet, a third or fifth of the total number of voxels may not produce integers (e.g. if total voxel count is 25 voxels, half of this will be 12.5. If this happens, round up the voxel count in favour of the anterior structure every time to ensure a consistent approach.

3. e.g. Total voxel count of CC length = 33, Half of CC length = 16.5, give Anterior half 17 voxels, and posterior half 15 voxels.
4. Or if AC/PC line has an uneven 1/3 number (e.g. AC/PC = 32, 1/3 = 10.7, use the following guidelines:

7.12.4 Common artefacts

Coronal NOTROI: These can be used for artefacts that protrude away from the expected shape of the segment. Sometimes artefacts protrude posteriorly form anterior segments or anteriorly from posterior segments (Fig.91). Other examples are artefact fibres from the IFOF or ILF. For some of the more anterior segments, there are often artefact fibres from the cingulum travelling in an anterior – posterior direction over the body of the corpus callosum. These can be removed using coronal NOTROIs (Fig. 91).

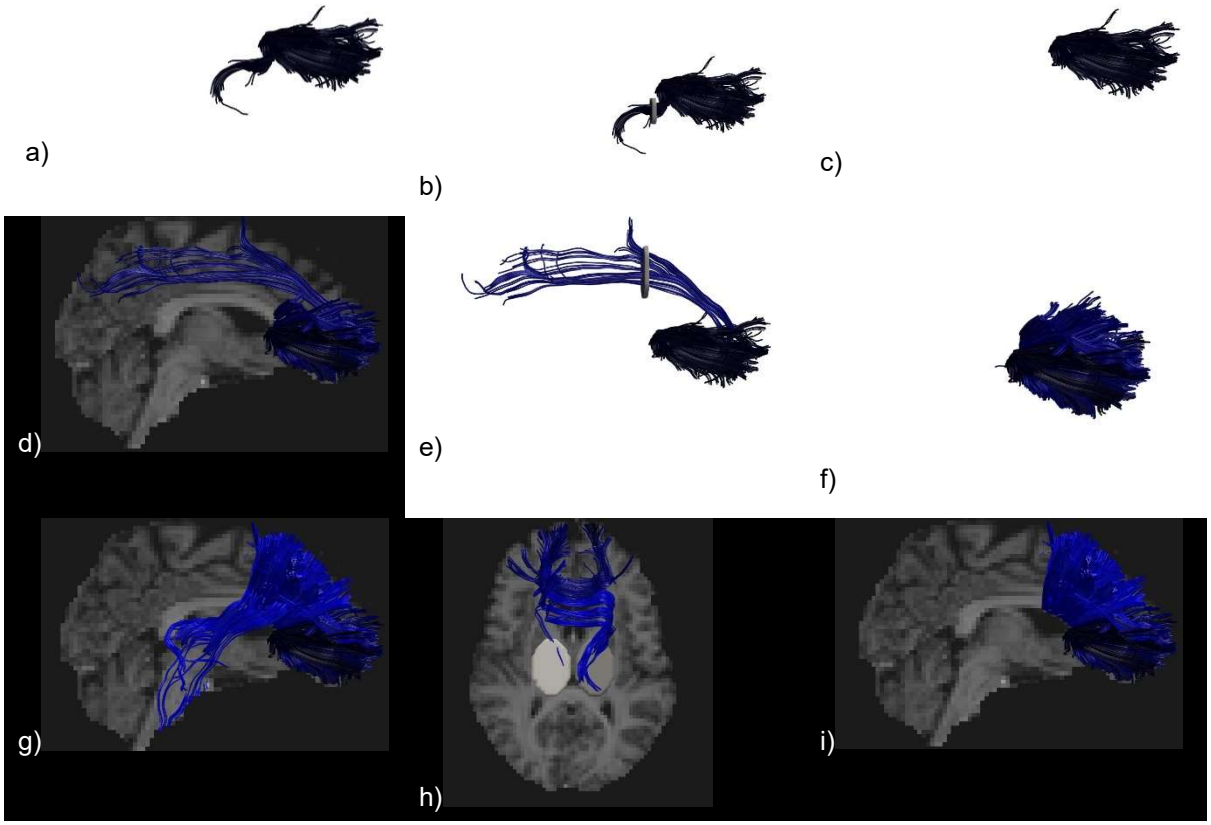


Figure 92 Coronal NOTROIs used to remove artefacts from corpus callosum

Projection artefacts: These can be removed using an Axial NOTROI (e.g. see Figs. 93 g - i and 94 d – f).

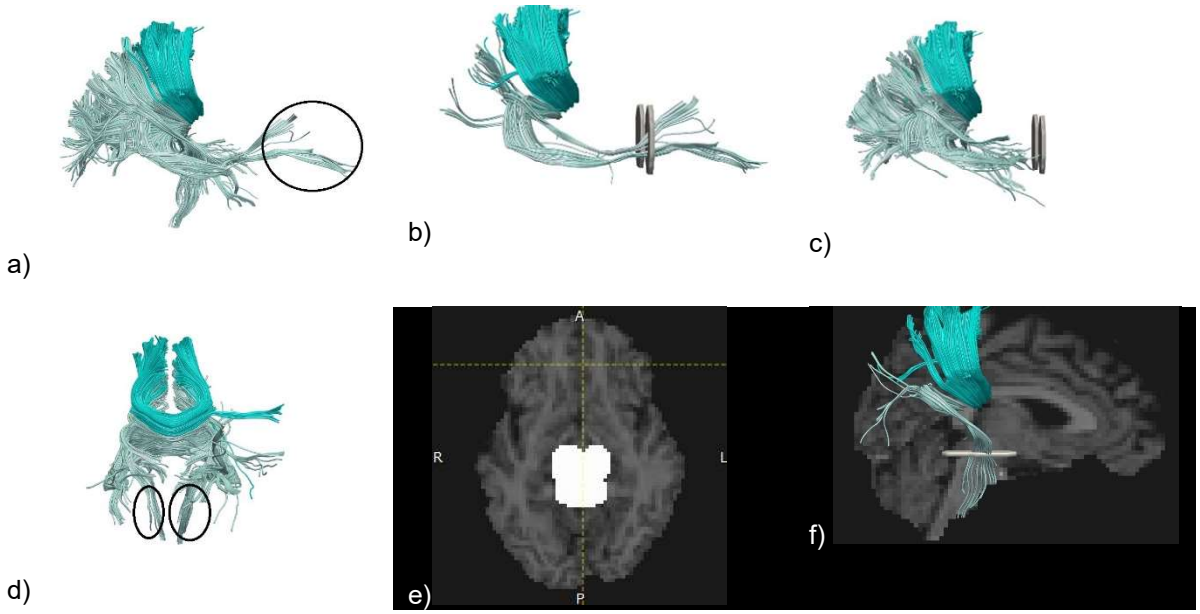


Figure 93 Axial NOTROIs used to remove artefacts from corpus callosum

7.13 Frontal Aslant Tract

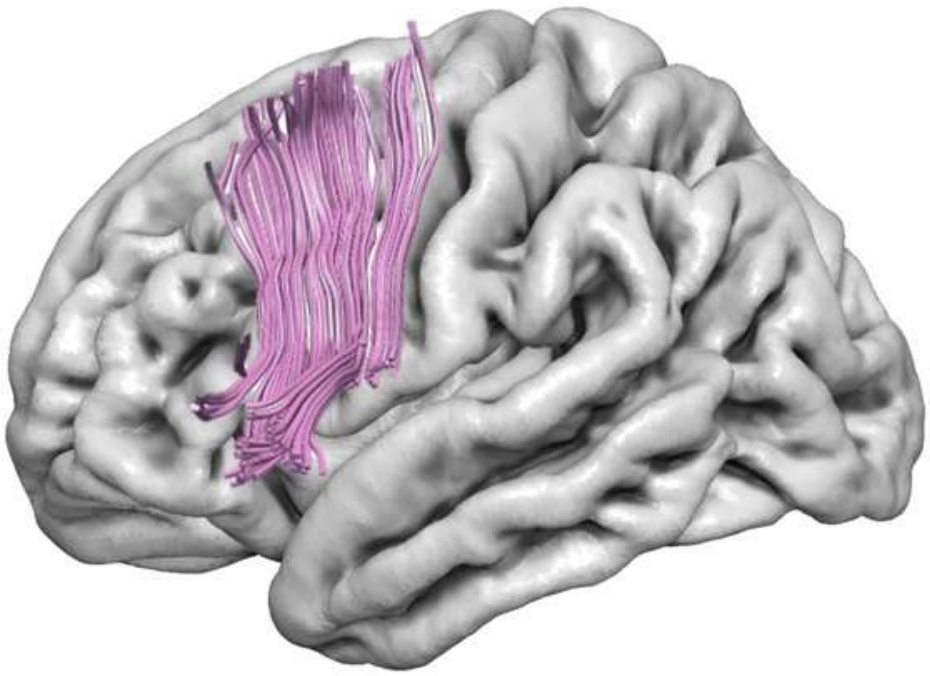


Figure 94 Drontal aslant tract, lateral view

7.13.1 Regions of interest

Table 28 List of Regions of Interest (ROI) for FAT

	Region of interest	Description
1	FRONT OP ANDROI Left	A sphere ANDROI
2	SMA ANDROI Left	A hand drawn ANDROI positioned on axial slice
3	NR Sag1 Left	Not ROI positioned in the sagittal midline to prevent artefact fibres crossing hemispheres
4	NR Ax1 Left	Not ROI positioned on the axial plane to cut out artefact fibres crossing with projection tracts

7.13.2 Step by step instructions

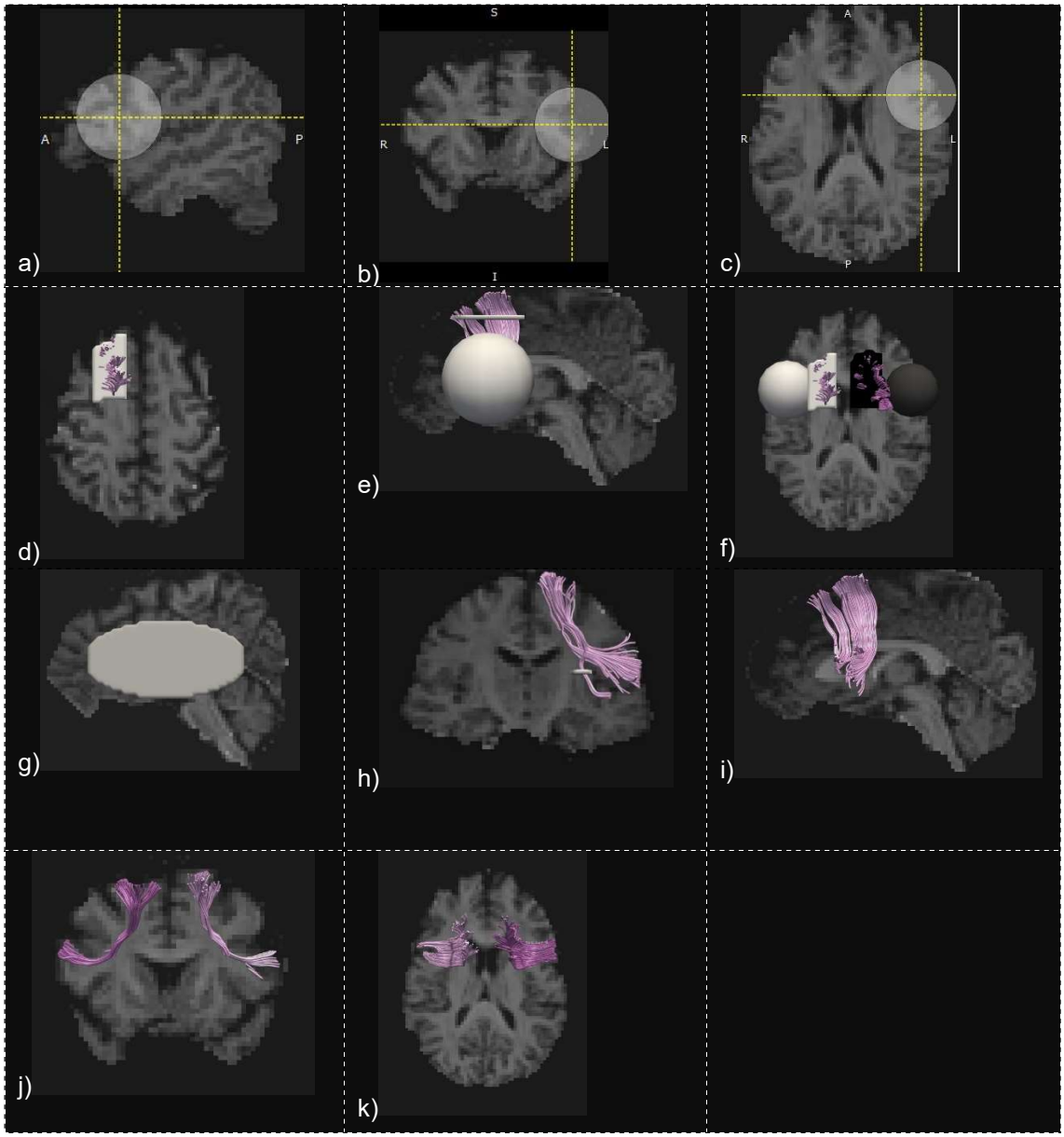


Figure 95 FAT dissection protocol

1. **Draw Frontal opercula sphere ANDROI:** Using the sagittal plane, locate the Frontal-Operculum (BA44), pars triangularis (BA45) and some of the precentral gyrus (BA4) and create a sphere ROI. Increase the radius to approximately 8 – 9, ensuring it encapsulates the 'V' of the pars triangularis (Fig. 95a - c). Create tract group FAT Left from this ANDROI.
2. **Draw SMA ANDROI:** Go to the axial plane and move the view until the dorsal termini of the FAT are visible. Hand draw anterior around these fibres being careful to keep within the boundary anterior to the precentral gyrus (Fig. 95d).
3. **Finalise AND ROI assignments for tract**: Go to tract and toggle with SMA ANDROI. Then assign the Front Op ANDROI as 'Either End'. Assign the SMA ANDROI as 'Any Part'.

7.13.3 Common artefacts

Sagittal NOTROI: Draw CC NOT ROI using the sagittal plane at the midline to remove any fibres crossing the midline.

Axial NOTROI: If there are artefact fibres that have crossed with projection fibres use Axial NOTROI's to remove them (Fig. 95h)

7.15 Inferior Fronto Occipital Fasciculus

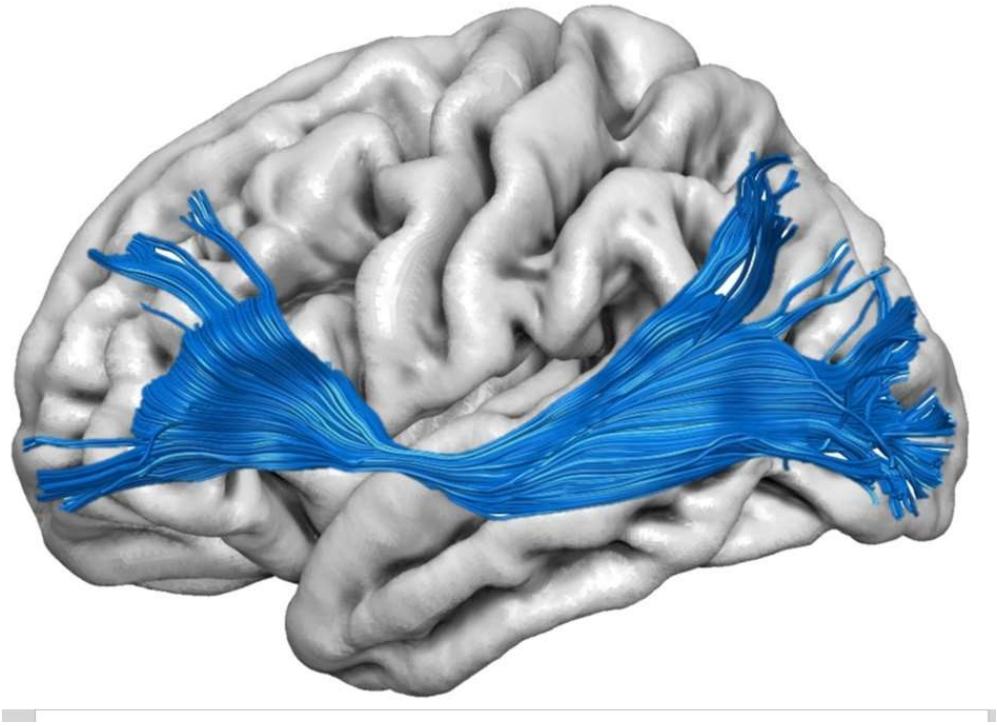


Figure 96 The inferior fronto-occipital fasiculus (IFOF)

7.15.1 Regions of interest

Table 29 List of Regions of Interest (ROI) for IFOF

	Region of interest	Description
1	FRONT ANDROI	Frontal ANDROI positioned on an anterior coronal slice
2	OCC ANDROI	Occipital ANDROI positioned on a posterior coronal slice
3	NR SAG	Sagittal NOTROI to remove commissural artefacts
4	NR COR	Coronal NOTROI
5	NR AX	Axial NOTROI to remove projection artefacts.

7.15.2 Step by step instructions

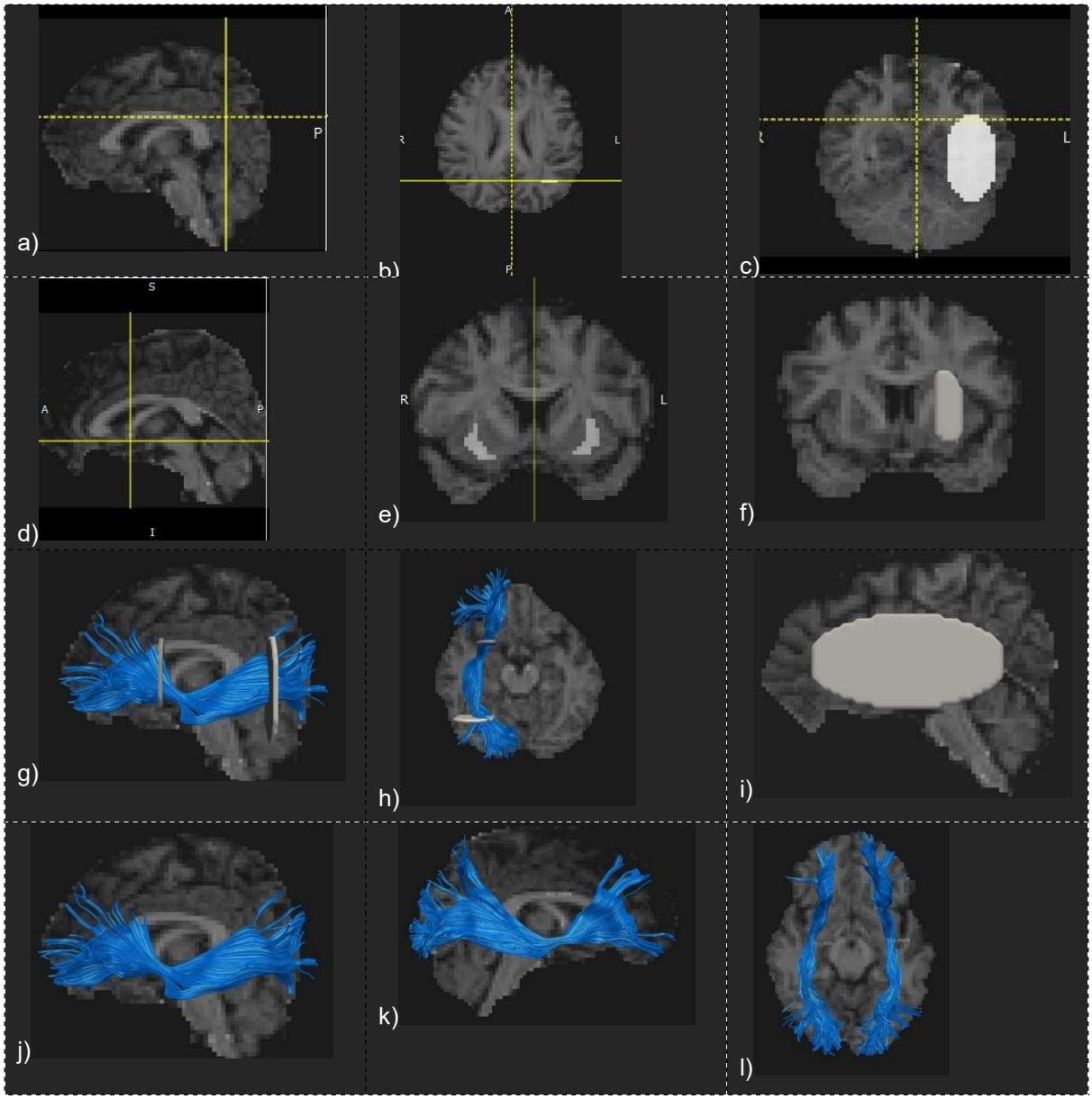


Figure 97 IFOF dissection protocol

1. **Orientation:** Go to sagittal slide and locate midline (by viewing on coronal slice).
2. **Occipital ANDROI:** Locate the most posterior point of the splenium of the corpus callosum. Place the coronal slice there and move back 4 slices (Fig. 97a – b). On this slice, create large oval ROIs in the Occipital lobe (Fig. 97c). The most posterior tip of the horn of the lateral ventricle may or may not be present depending on the individual. Create track from this ANDROI.
3. **Frontal ANDROI:** Go back to the sagittal slice and find the anterior commissure at the foot of the fornix (Fig. 97d). Place the coronal cross hairs here and move 2 coronal slices forward (anterior). On this coronal slice position the frontal ROIs (Fig. 97 e – f). These will

be smaller ovals that cover the narrow section of the IFOF before it fans out into the more anterior sections of the Frontal lobe.

4. **Toggle** respective Occipital ROIs with Frontal ROIs**.**

7.15.3 Common artefacts

For artefact fibres crossing into the contralateral hemisphere use a Sagittal NOTROI (Fig. 97i).

For artefact fibres crossing with the cingulum, in an anterior / posterior direction use Coronal NOTROIs (Fig. 98).

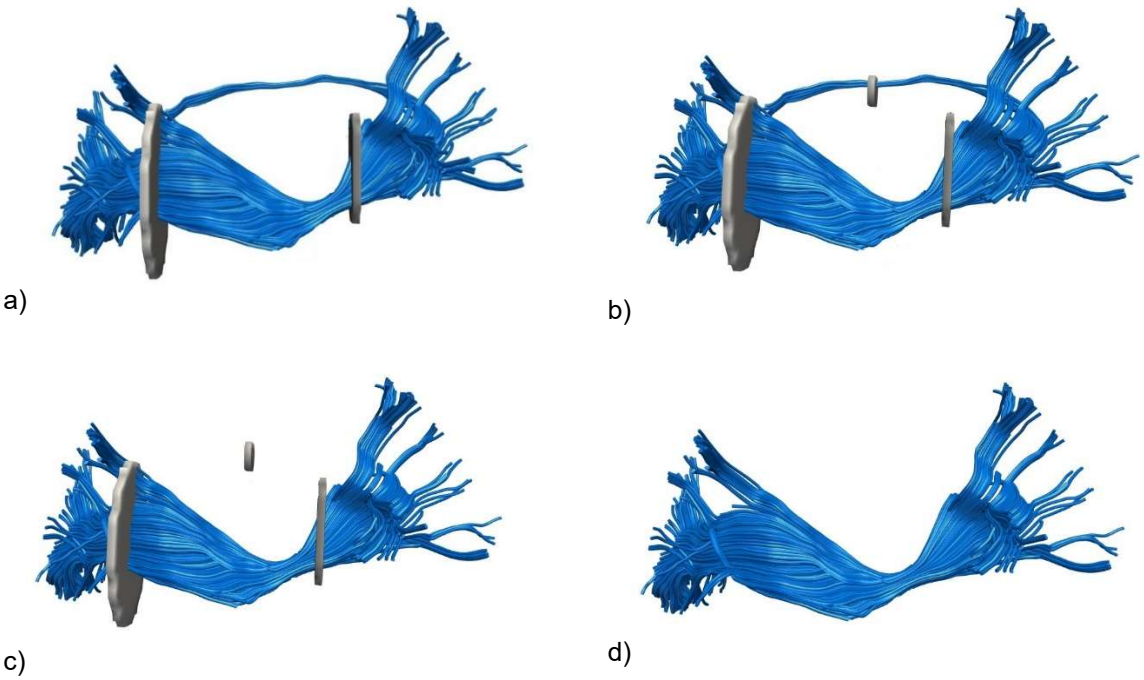


Figure 98 The use of a coronal NOTROI to remove artefacts from the IFOF

7.16 Superior Longitudinal Fasciculus

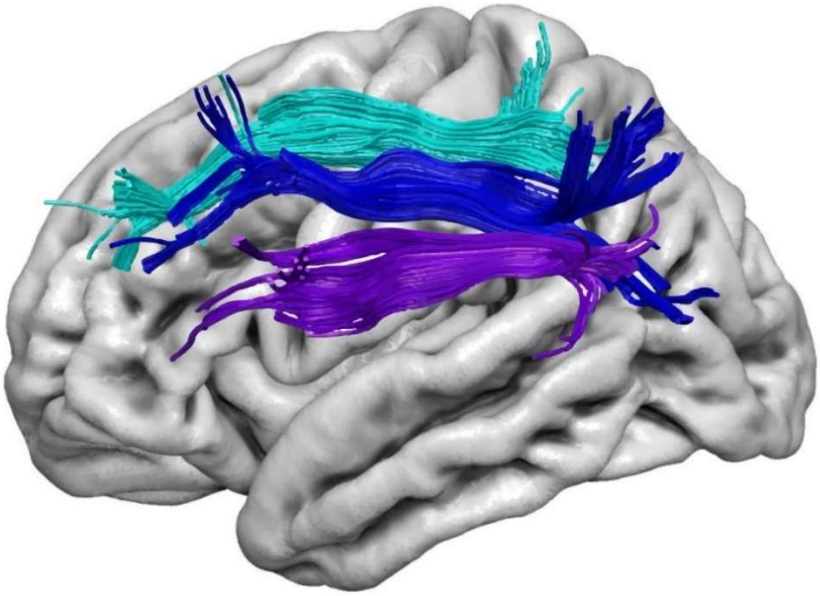


Figure 99 The superior longitudinal fasciculus (SLF) System

7.16.1 Regions of interest

Table 30 List of Regions of Interest (ROI) for SLF System

	Region of interest	Description
1	SFg ANDROI L	Superior Frontal Gyrus (for SLFI)
2	MFg ANDROI L	Middle Frontal Gyrus (for SLFII)
3	IFg ANDROI L	Inferior Frontal Gyrus (for SLFIII)
4	Par ANDROI L	Parietal ANDROI for all SLFI – III
5	Temp NR	Temporal NOTROI for all SLFI-III but impacts SLFIII the most
6	NR Sag1	Sagittal NOTROI
7	NR Cor1	Coronal NOTROI
8	NR Ax1	Axial NOTROI

7.16.2 Step by step instructions

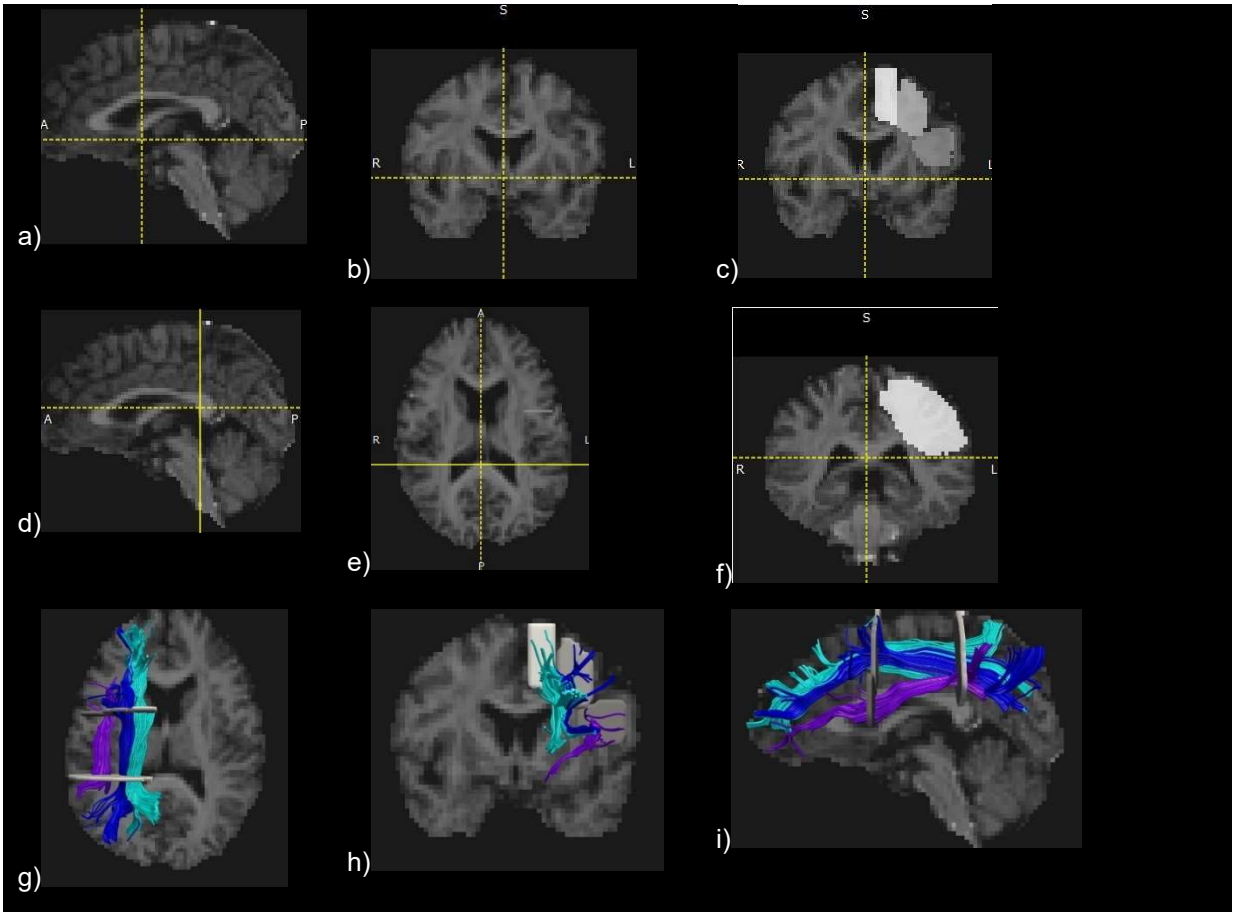


Figure 100 SLF system dissection protocol

- **Location of anterior ANDROIs:** On the midline sagittal slice locate the anterior commissure. If it positioned just below (ventral to) the tip of the fornix (Fig. 100a).
- **Creating the SFg ANDROI:** On the coronal section at the point of the anterior commissure, draw this ROI to cover white matter of the superior frontal gyrus. Make sure it does not go too deep to cover the cingulum. Repeat on one slice anteriorly and one slice posteriorly to create a ROI 3 slices thick (Fig. 100c).
- **Creating the MFg ANDROI:** On the same coronal section delineate white matter in the middle frontal gyrus. Repeat on one slice anteriorly and one slice posteriorly to create a ROI 3 slices thick.
- **Creating the IFg ANDROI:** On the same coronal section delineate white matter in the inferior frontal gyrus as per Fig. 100c. As before, repeat on one slice anteriorly and one slice posteriorly to create a ROI 3 slices thick.
- **Creating the Par ANDROI.** Go to the midline sagittal plane. Move 2-3 slices to the left until a clear view of the curve of the thalamus just posterior to the midbrain

becomes visible. Move the coronal slice to the most posterior limit of the thalamus. On the corresponding

coronal slice delineate the ROIs as per Figure 100f. Alternatively, use the axial plane at the dorsal point of the brain and identify the divide between frontal and parietal lobes and place the coronal slice at the most anterior limit of the post central gyrus (i.e. just within the parietal lobe).

- **Create tracts:** Create SLFI from SFg ANDROI. Toggle with Par ANDROI; Create SLFII from MFg ANDROI and toggle with Par ANDROI. Create SLFIII form IFg ANDROI and toggle with Par ANDROI.

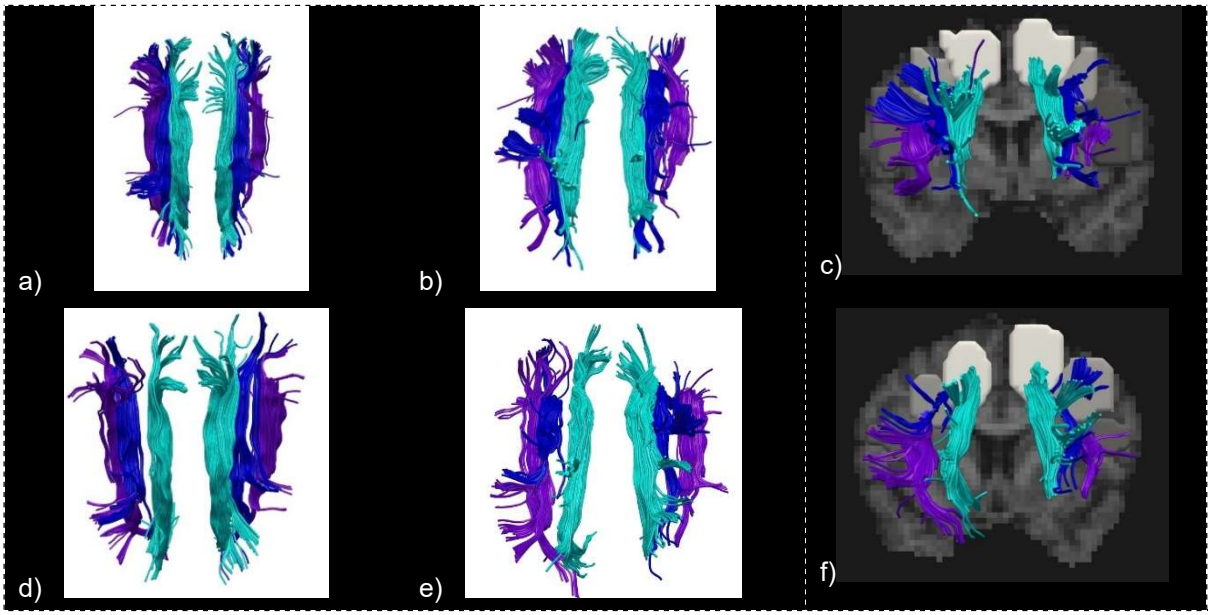


Figure 101 Examples of different SLII positioning between SLFI and SLFIII

- Once the tracts are created you will need to verify that the frontal ANDROIs have correctly separated out the tracts. Sometimes they are so close together it is difficult to distinguish between SLFI and SLFII or SLFII and SLFIII. One way to do this is to view the frontal termination points of each tract (Fig. 101)
- **Create Temp NOTROI:** Go to the coronal slice with the Parietal ANDROI positioned on it (Fig. 101b). Identify the gap between the base of the parietal lobe and the dorsal limit of the temporal lobe (Fig. 101c). Then look for the axial slice cutting across the dorsal limit of the temporal lobe that has the *most* continuous bright voxels along its horizontal line. Go to the axial slice once positioned and draw the temporal NOTROI (Fig. 101d). It will cover the lower quadrant of the brain. **It's important to be aware**

that being inconsistent in the way the temporal NOTROI is positioned can lead to dramatic differences in SLF volumes.

- **Toggle Temp NOTROI** with all tracts in that hemisphere and set to 'NOT' (Fig 102g-i).

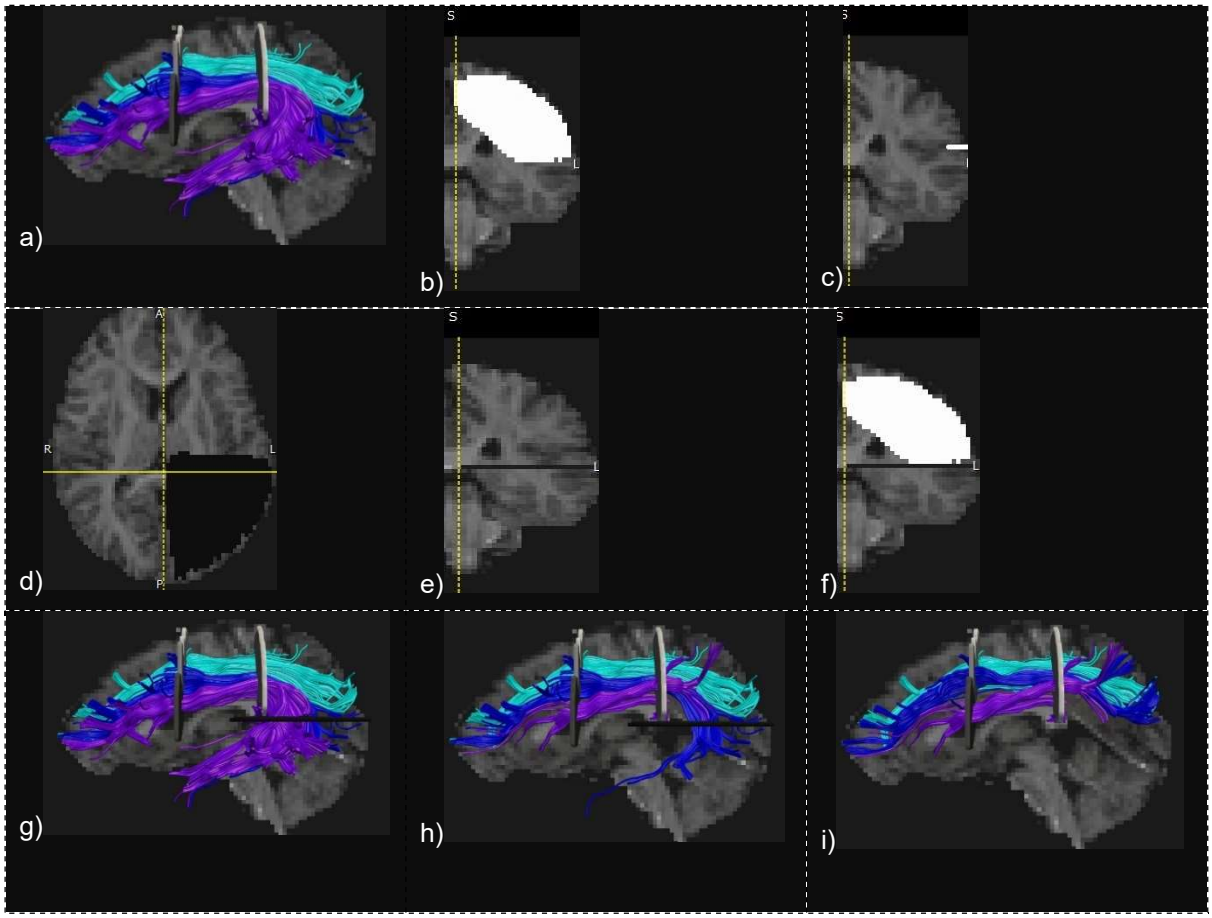


Figure 102 Positioning of temporal NOTROI for SLF system

7.16.3 Common artefacts

Sagittal NOTROI: If needed to remove fibres crossing to the contralateral hemisphere, use a large oval sagittal NOTROI positioned over the corpus callosum at the midline sagittal slice. **Coronal NOTROIs** can remove artefact fibres from neighbouring tracts like the cingulum. **Axial NOTROI** can remove frontal 'hooks' similar to those seen in the cingulum (Fig 103).

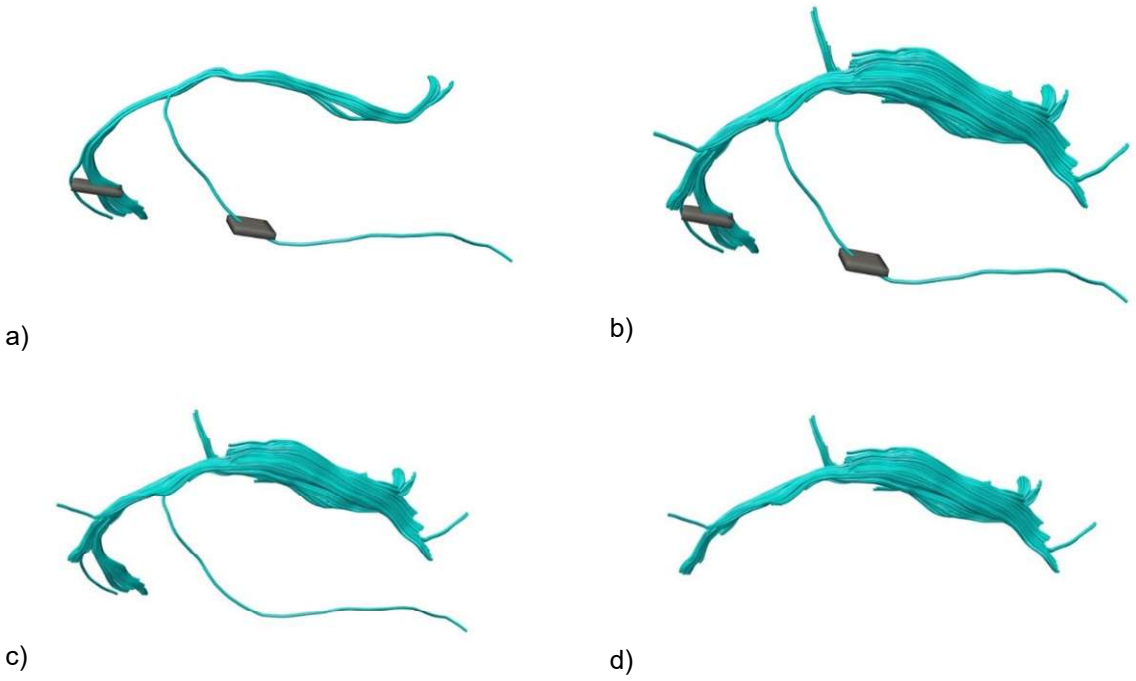


Figure 103 Frontal 'hook' and projection artefact removed by a axial NOTROIs

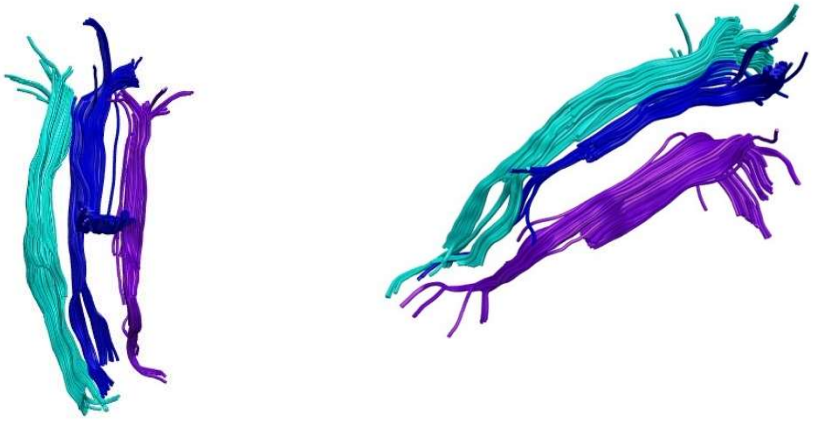
7.16.4 Inter-Individual variation in SLF anatomy

From the data set used in Chapter 4 some informal observations were made regarding patterns of variability in the SLF system. In the left hemisphere, just under a third (28%) of SLFII tracts were positioned equidistant SLFI and SLFIII. Over a half were aligned more closely to SLFI than SLFIII compared to only 11% that were aligned closer to SLFIII and in 2 of the 18 individuals there was no SLFII visible at all.

For the right hemisphere, a higher percentage of SLFII were equidistant between SLFI and SLFII (44%), half were aligned more closely to SLFIII and only 6% were aligned more closely to SLFI. There were no missing SLFII tracts in the right hemisphere.

a) Equidistant

b) Closer to SLF



c) Closer to SLFIII

d) No SLFII in left hemisphere

Figure 104 Illustrations of four different arrangements of the SLF system.

It was possible to distinguish separate frontal termination points between tracts for 78% of individuals in the left hemisphere but for a small percentage (11%) it was difficult to differentiate between tracts. In the right hemisphere, 72% of individuals were observed to have separate frontal termination points between tracts and a slightly higher percentage (28%) were difficult to separate out by eye.

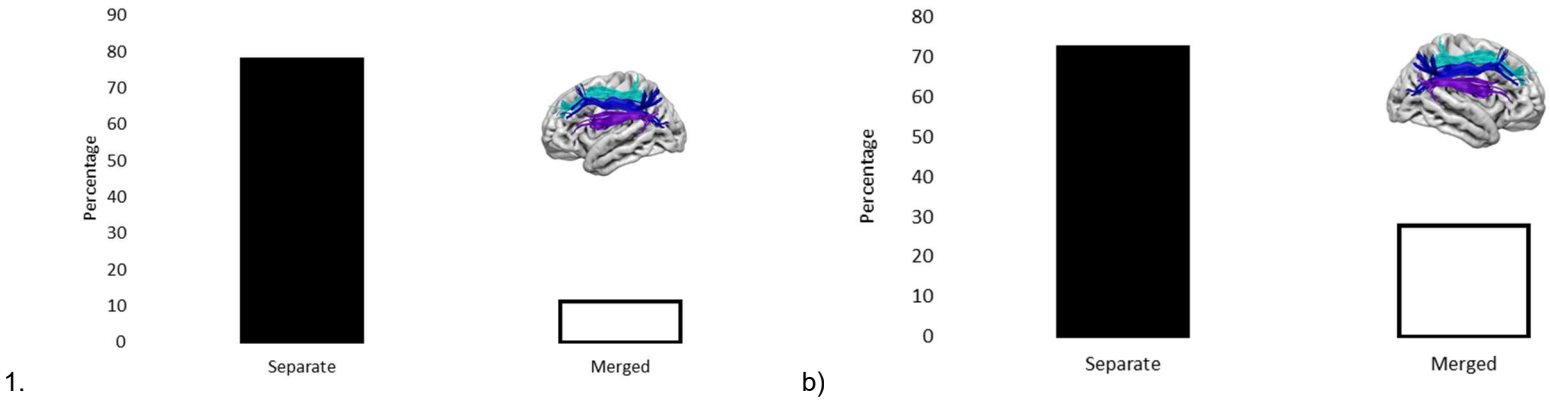


Figure 105 Different frontal termination points separate or merged for a) left and b) right hemispheres

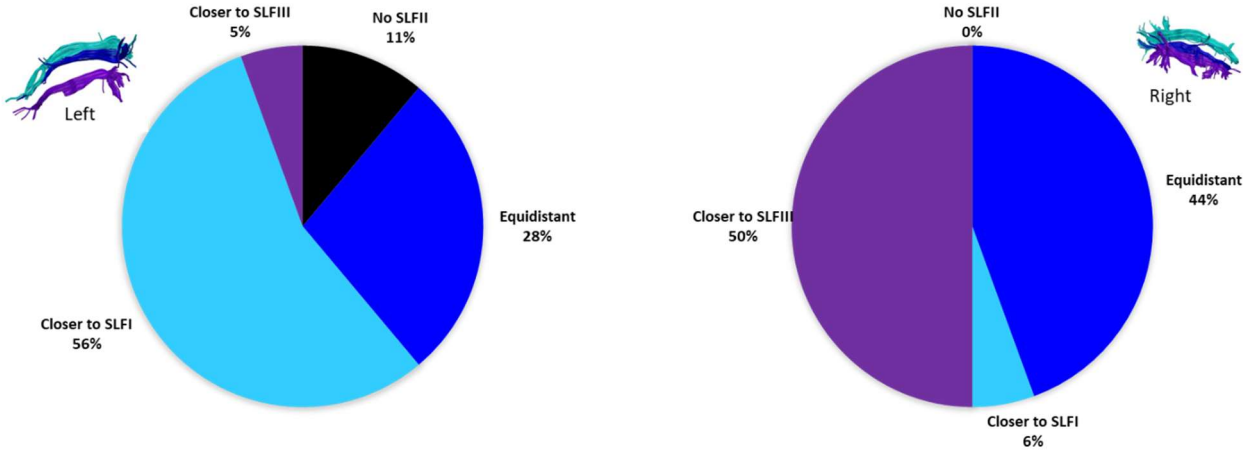


Figure 106 Different SLF system arrangements across individuals per hemisphere

7.17 Uncinate

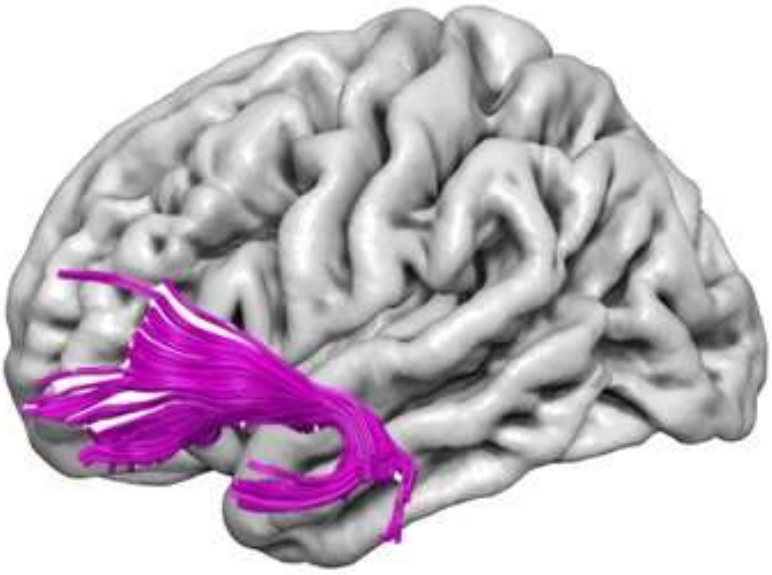


Figure 107 The uncinate Fasiculus

7.17.1 Regions of interest

Table 31 List of Regions of Interest (ROI) for uncinate

	Region of interest	Description
1	Front UNC	Frontal ANDROI
2	Temp UNC	Anterior Temporal ANDROI
3	Sag NR	Sagittal NOTROI
4	Cor NR	Coronal NOTROI
5	Ax NR	Axial NOTROI

7.17.2 Step by step instructions

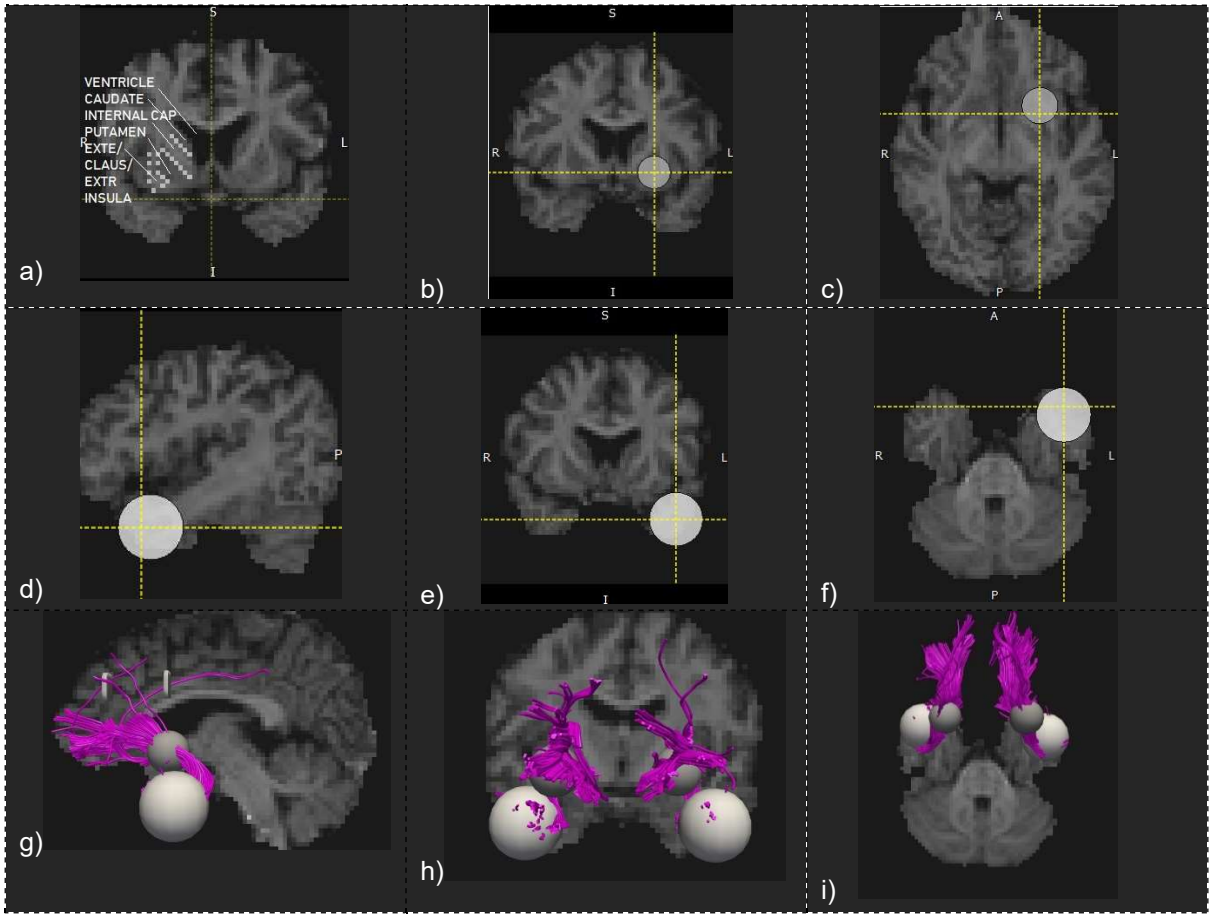


Figure 108 uncinate dissection protocol

1. **Orientation:** Look for the floor, or most ventral point of the external / claustrum / extreme capsule grouping (Fig. 108a). With finer resolution, these will be visualised by a light/grey/light set of strips on the coronal section. However, the maps for Spherical Deconvolution and DTI do not have sufficient resolution, and these three structures merge into one white matter region. At the base of this grouping, the uncinate fibres travelling in an anterior / posterior direction are found. More dorsal within this grouping, the IFOF fibres travelling in the same direction are found.
2. **Frontal ROIs:** Create a sphere ROI and place it at the base of the External/Claustrum/Extreme capsule grouping (as described above) (Fig. 108b – c).
3. **Temporal ROIs:** On the same coronal plane, create two more spheres, in the anterior temporal lobes. Increase the radius of these spheres until they fill fully the anterior section of the temporal lobe. The posterior boundary of the anterior temporal lobe can be checked on a sagittal slice (Fig. 108 d - f).

Create the track from the frontal ROI. Toggle with the Temporal ROI to visualise the main uncinate track and any artefact fibres (Fig. 108a-d).

7.17.3 Common artefacts

Anterior commissure: Remove with UNCNR Sag1 (Fig. 109 a – d).

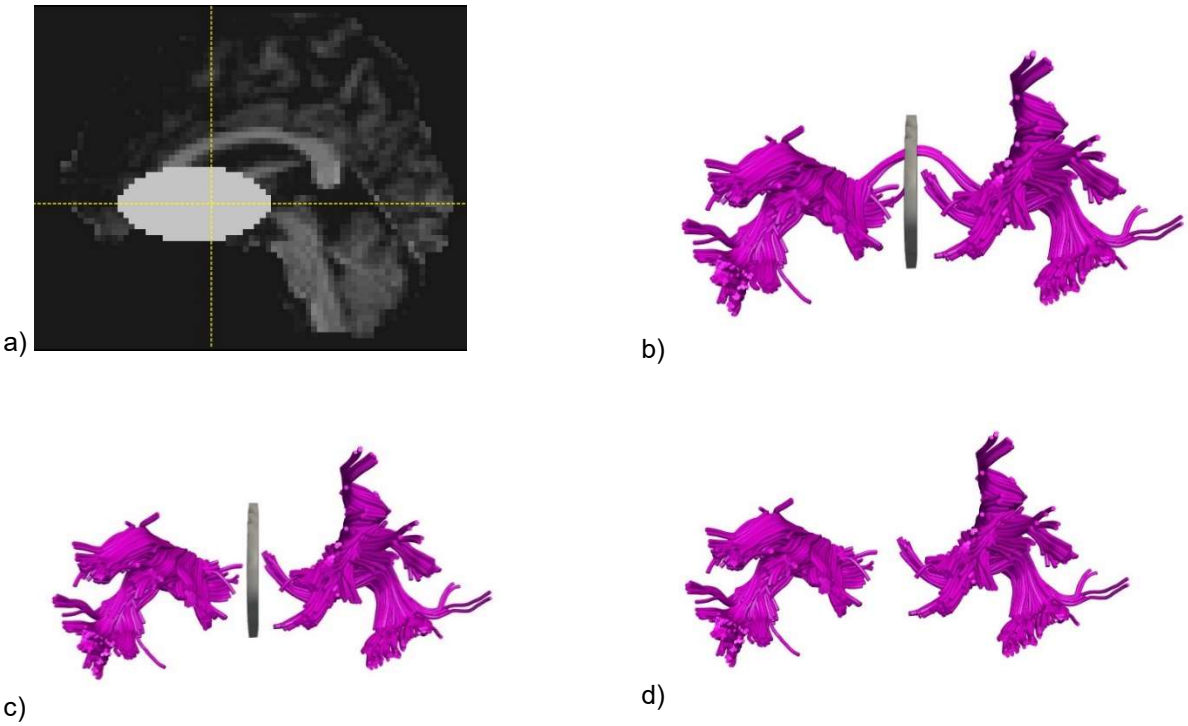


Figure 109 Commissural artefacts removed by a sagittal NOTROI

IFOF / cingulum or other anterior – posterior artefacts Remove with UNCNR Coronal (Fig. 110a – b)

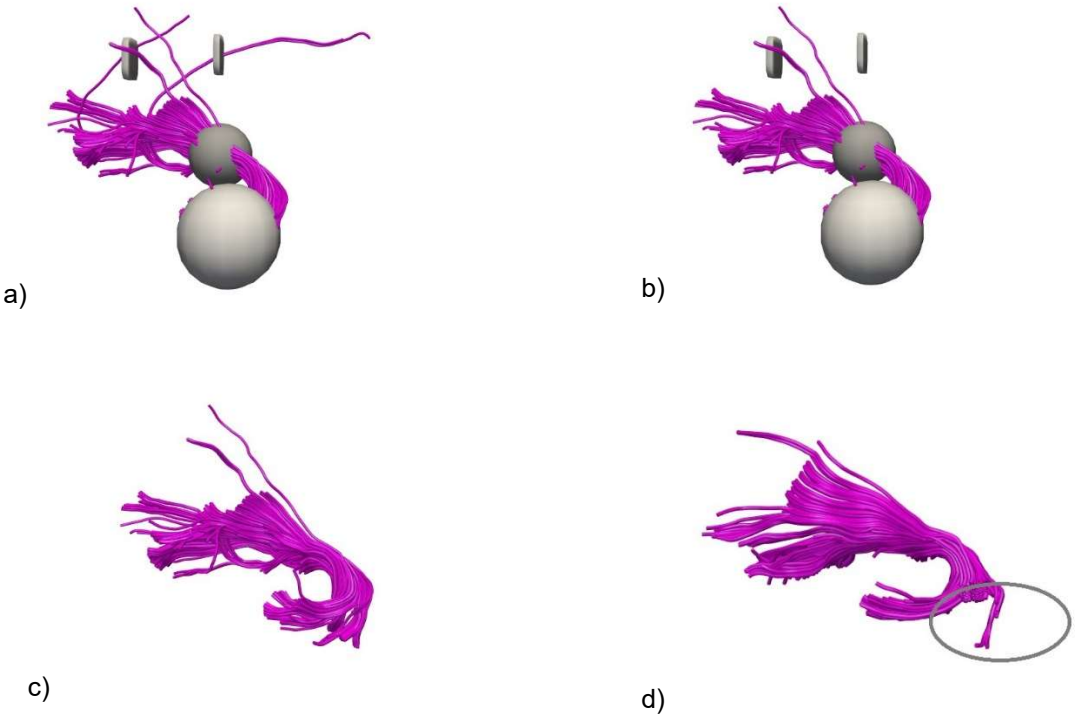


Figure 110 Artefacts of the uncinate removed by Coronal NOTROIs or left in place

Posterior temporal branching: There are sometimes minor branches reaching posteriorly from the uncinate's central hook shape. This protocol left these branches in place (Fig. 110c-d).

7.18 Mega Track instructions

Mega Track Dissection Guidelines

These guidelines were written after advice from Mega Track technical team.

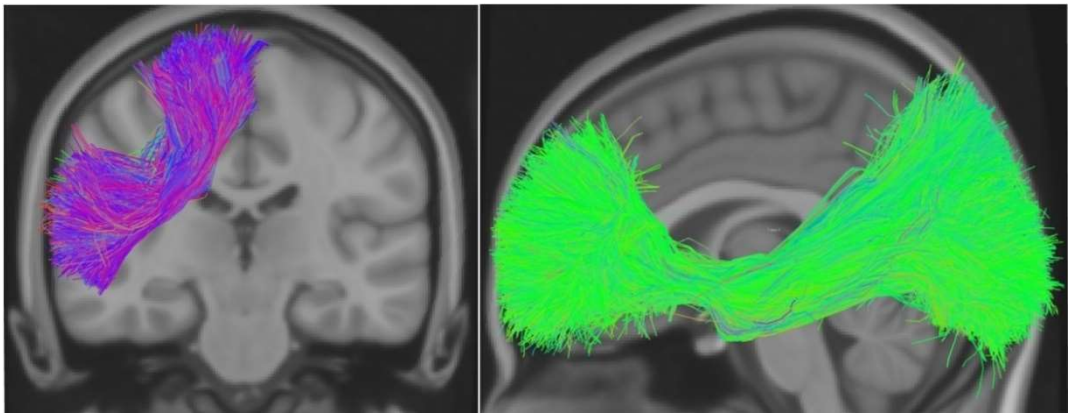


Figure 111 Examples of Mega Track FAT and IFOF tracts

- **Mega Track files**

Once your data set has been pre-processed and generated into Mega Track format, depending on the size of your data set, your Mega Track data will consist of either a single track file, or 3 – 5 track files (divided by lobe, hemisphere and tract group); an MNI template, and log files. A small data set of 20 subjects for example, will fit into a single Mega Track file; A large dataset of 150 subjects may need to be provided in separate sections (see below);

- Track file(s)
- MNI Template
- Log (text file describing the key parameters used in processing the Megatrack file)

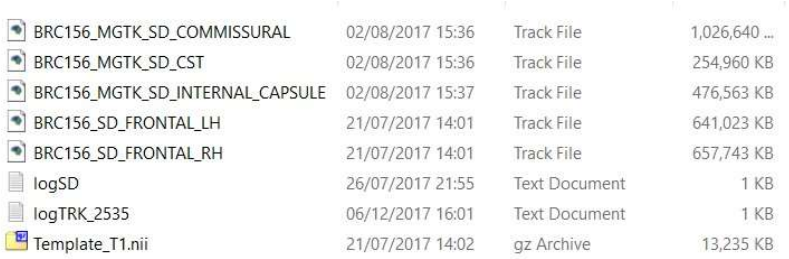


Figure 112 Mega track file formats

For example, the file 'BRC156_SD_FRONTAL_LH will include data to re-create all association tracts originating/terminating the frontal lobe of the left hemisphere; whereas,

BRC156_MGTK_SD_COMMISSURAL will include data required to dissect all commissural pathways.

- **Setting up the folder system**

For each tract you plan to dissect, create a folder with the Tract name, for example ‘FAT’ or ‘uncinate’. Inside this folder create 2 other folders, entitled ‘AND’ and ‘NOT’. Within them you will save (one at a time) each ‘AND’ and ‘NOT’ ROI required to create the tract. There is no limit on the number of AND or NOT ROIs that can be saved per tract, but for CUT ROIs only two ROIs can be saved per tract. When naming your nifty (.nii) ROIs, there should be no gaps (spaces).

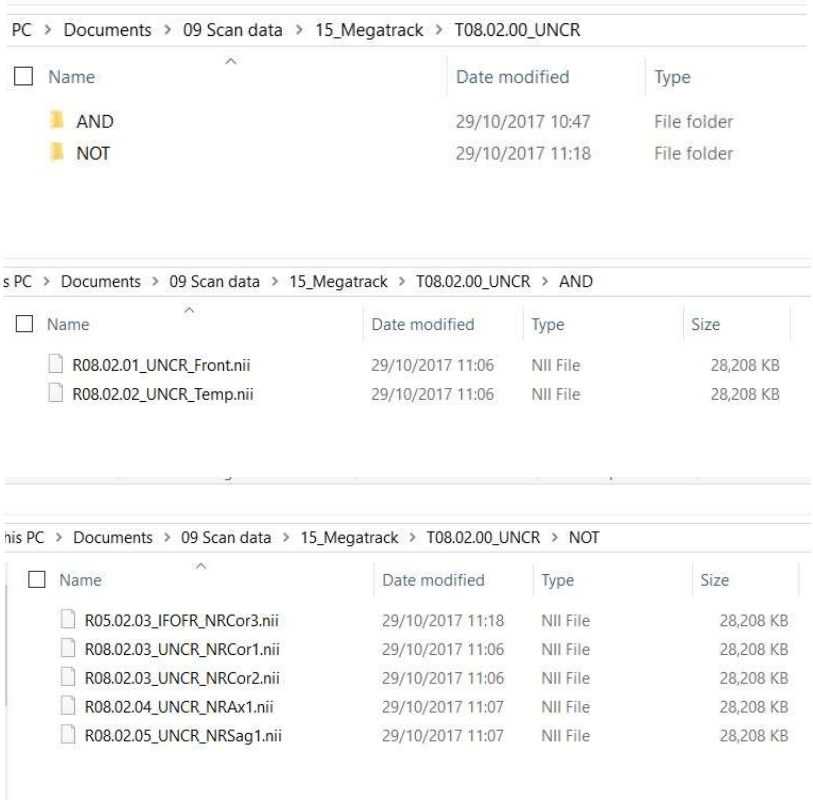


Figure 113 Example of folder structure for Mega Track dissection per tract

It is **important** to name these folders exactly as described as this will impact the processing of the dissections at a later stage. If the folder is not named correctly, the processing will not be conducted correctly.

- **Dissecting tracts**

Open TrackVis as normal. Load your tract file of interest (e.g. BRC156_SD_FRONTAL_LH) Load the MNI template as your 'Map' (Fig.114, circled in purple). Be aware that to start with the Mega Track Loads in a 'skipped' form – i.e. not all the fibres are visible. To make sure you dissect all fibres, you need to un-check the 'skip' box (Fig. 114, blue square). Create your ROI as you would normally with the following restrictions:

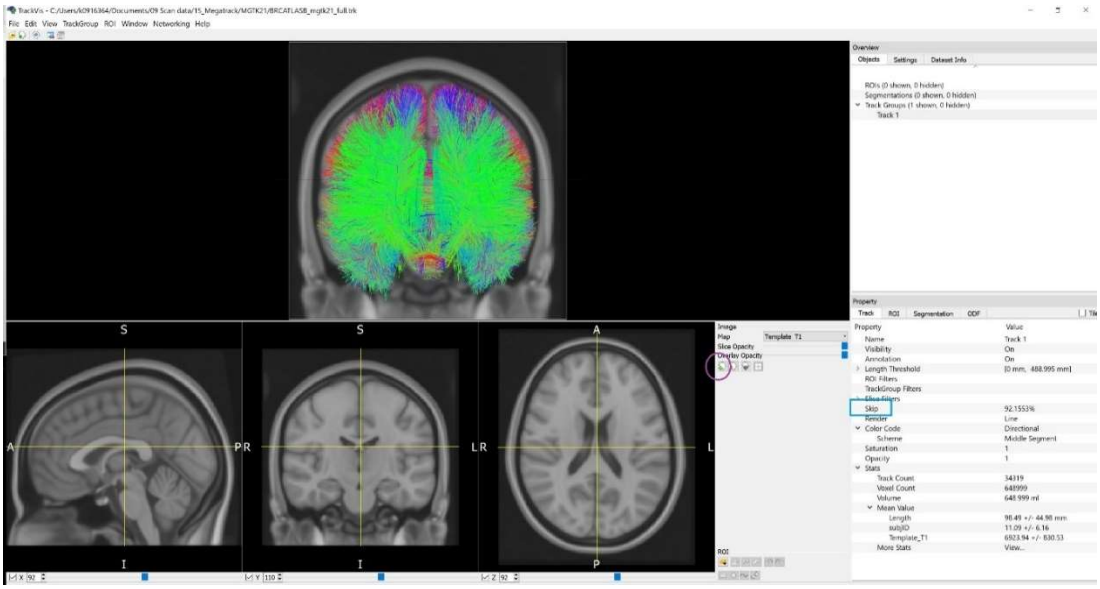


Figure 114 Loading of track file, MNI T1 Template into TrackVis 'Skip' setting

Restrictions

- You can only use AND, NOT [or CUT] ROIs for Mega Track;
- ROIs must be hand drawn, you cannot use Spheres or Disks.
- It is recommended that AND ROIs need to be at least 3 slices thick and NOT ROIs are at least 2 slices thick.
- It is recommended that each ROI needs to be saved individually, one at a time under its appropriate folder.
- When creating your tract, it is not possible with Mega Track to restrict tract length.

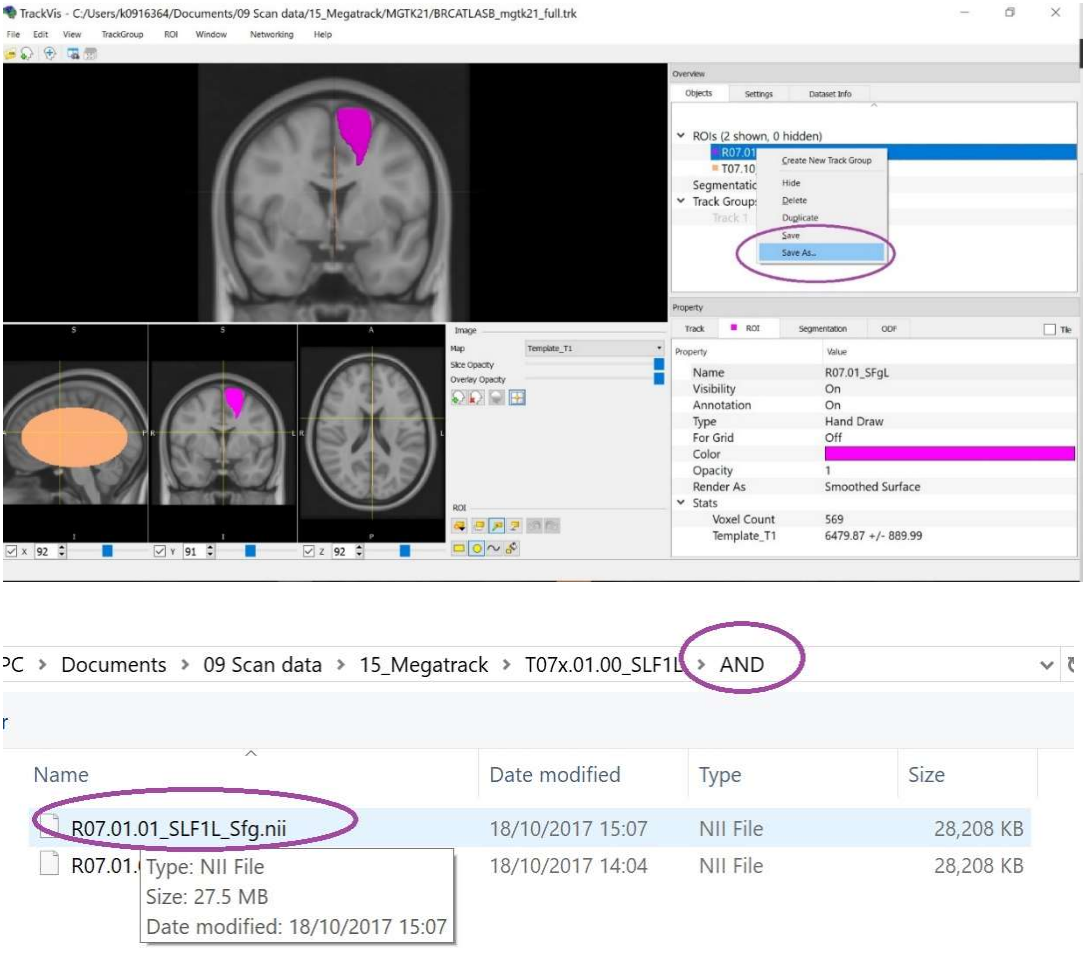


Figure 115 Saving ROIs under correct folder structure

NOT ROIs and artefacts

As Mega Track is a system that merges data from numerous participants, the number of artefacts is much larger than if you were to dissect tract on one individual brain. This means that you may need to create more NOT ROIs than you may be used to. It is important however to ensure all artefact fibres are removed before sending the dissection to be processed. As with dissection on individual files, use of NOT ROIs can removed both artefact and a percentage of anatomically legitimate fibres. It is recommended that you follow a documented protocol of both ANDROI and NOT ROI positioning.

Saving scenes

Depending on the size of your data set, a scene may be saved successfully, or it may become corrupted. Do not rely on saved scenes. Always save each ROI individually under its appropriate folder before closing Track Vis, or you will lose the work you have done. This means that you will

have to re-create tracts from saved ROIs each time you open Track Vis (e.g to create images for example).

Time lag

Again, depending on the size of the data set, there may be a second or two delay in opening the main track, saving each ROI or generating tracks from ROIs.

Completed dissections

Once you have dissected all the tracts you want, and saved all ROIs under the relevant folder structure, you can zip the file and send it to a member of the Mega Track team [or process yourself] to be processed.

Output

Once the dataset has been processed, you can expect two types of output files:

- A single spreadsheet file for each tract listing key parameters per participant/individual (Fig. 116).
- Depending on the number of participants included in the Mega Track it is possible to locate individual tract files generated by Mega Track but these may not be provided initially.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
	sul	Trackfile	Pti	track_cour	voxel_cour	volume_m	MD_mean	MD_mean	HMOA_1_r	HMOA_1_s	AngTrk_me	AngTrk_std	AP6np1_m	AP6np1_std
1		BRCATLAS	1	177	1193	9.544	0.512305	0.540488	0.018901	0.012205	4.668891	3.548183	-999	-999
2		BRCATLAS	2	95	719	5.752	0.511516	0.542295	0.01674	0.008205	4.487879	3.527612	7.131751	0.724897
3		BRCATLAS	3	223	1204	9.632	0.517068	0.54051	0.021462	0.012288	3.980455	3.44672	7.212295	0.86117
4		BRCATLAS	4	200	1283	10.264	0.533314	0.567477	0.017636	0.011411	4.654219	3.792233	7.056142	0.920307
5		BRCATLAS	5	112	964	7.712	0.516901	0.546213	0.01833	0.01048	4.726251	3.700289	-999	-999
6		BRCATLAS	6	124	918	7.344	0.522431	0.552866	0.016727	0.008714	4.264592	3.622234	7.066462	0.768633
7		BRCATLAS	7	276	1542	12.336	0.539055	0.559586	0.019373	0.016437	4.010067	3.3505	-999	-999
8		BRCATLAS	9	174	996	7.968	0.537219	0.564293	0.01698	0.009193	4.381382	3.4729	7.006665	0.844418
9		BRCATLAS	#	456	1652	13.216	0.512368	0.545847	0.021025	0.009549	4.022666	3.104871	7.244243	0.884498
10		BRCATLAS	#	184	775	6.2	0.512589	0.557999	0.021075	0.011745	4.375259	3.697044	7.226433	0.927105
11		BRCATLAS	#	90	686	5.488	0.522766	0.545423	0.015658	0.007384	4.696666	3.736623	6.970843	0.747695
12		BRCATLAS	#	206	1012	8.096	0.509723	0.527842	0.017624	0.011323	4.514579	3.719111	-999	-999
13		BRCATLAS	#	122	847	6.776	0.513886	0.540103	0.016534	0.00802	4.476636	3.768228	7.021362	0.853163
14		BRCATLAS	#	307	1187	9.496	0.508194	0.545981	0.0188	0.013385	4.400407	3.519918	7.241822	0.823314
15		BRCATLAS	#	44	584	4.672	0.518582	0.530987	0.017995	0.010498	4.594785	3.696166	7.104326	0.817291
16		BRCATLAS	#	157	770	6.16	0.517378	0.543026	0.020801	0.017915	4.097338	3.462147	7.107106	0.938337
17		BRCATLAS	#	211	1129	9.032	0.516612	0.552296	0.020354	0.014832	4.163532	3.600782	7.27841	0.856231
18		BRCATLAS	#	35	395	3.16	0.507603	0.527957	0.015851	0.013157	4.970652	3.97419	-999	-999
19		BRCATLAS	#	31	430	3.44	0.529912	0.553011	0.016703	0.009616	4.654486	4.13581	7.017367	0.897168
20		BRCATLAS	#	79	841	6.728	0.518797	0.541743	0.01817	0.032307	4.582988	3.835979	-999	-999
21		BRCATLAS	#	320	1321	10.568	0.523501	0.548378	0.01937	0.011125	4.029079	3.269906	-999	-999
22		BRCATLAS	#	22	294	2.352	0.498184	0.512484	0.021386	0.013584	4.669357	4.017115	7.343256	0.910888
23		BRCATLAS	#	134	840	6.72	0.515465	0.543838	0.01932	0.074147	4.727002	3.451629	7.114802	0.882106
24		BRCATLAS	#	32	373	2.984	0.504431	0.527581	0.019533	0.011008	4.123446	3.298169	7.243017	0.839475
25		BRCATLAS	#	66	723	5.784	0.520489	0.551417	0.017541	0.012729	4.188767	3.655288	7.025084	0.939499
26		BRCATLAS	#	35	399	3.192	0.514716	0.53208	0.01414	0.008054	5.069041	3.901648	6.998003	0.813052
27		BRCATLAS	#	131	664	5.312	0.555361	0.571598	0.016479	0.009798	4.370658	3.753243	7.016973	0.746579

Figure 116 Mega Track output spreadsheet example

7.19 Megatrack dissection examples

7.19.1 Corpus callosum

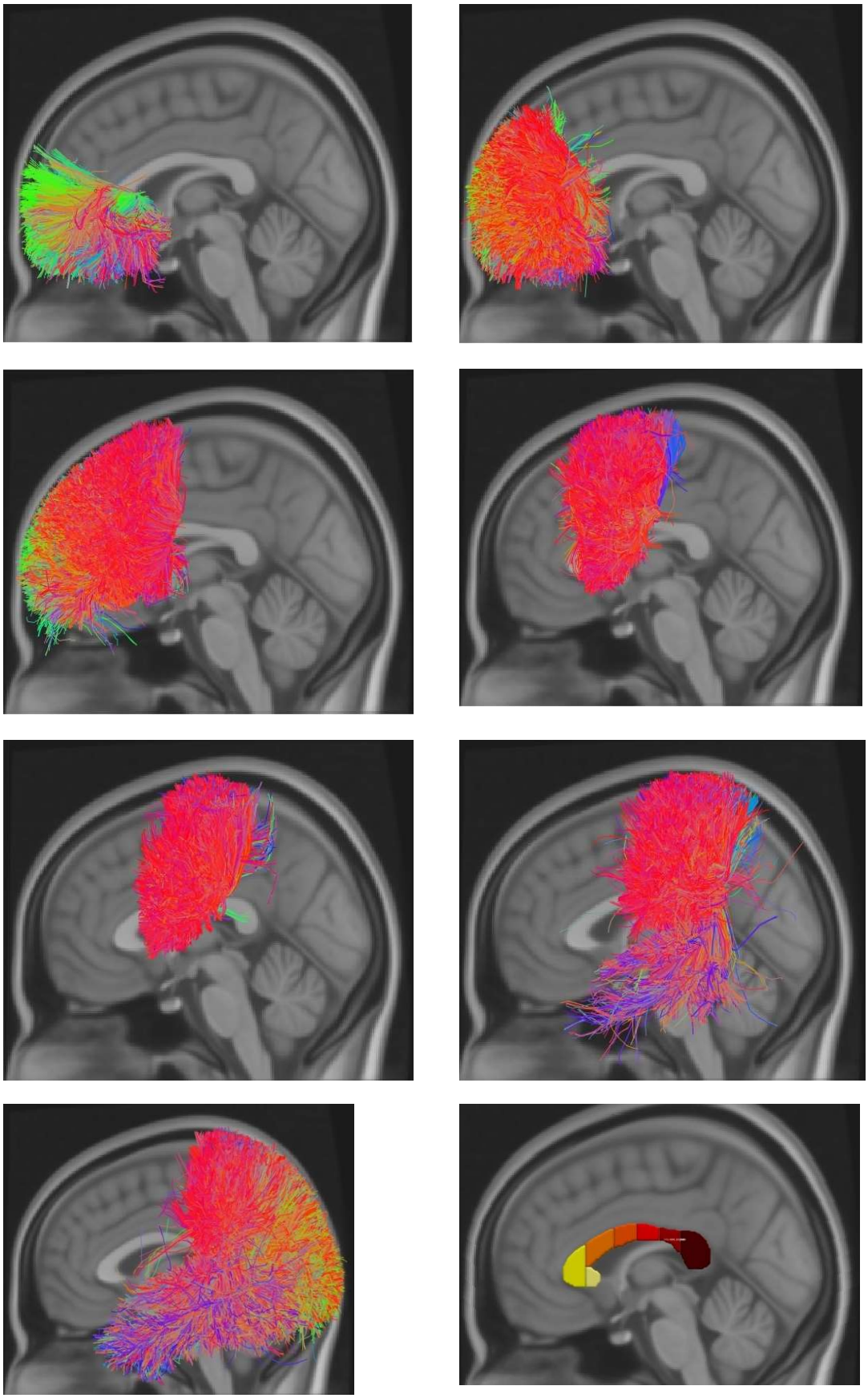


Figure 117 Megatrack Corpus callosum segments

7.19.2 Cingulum

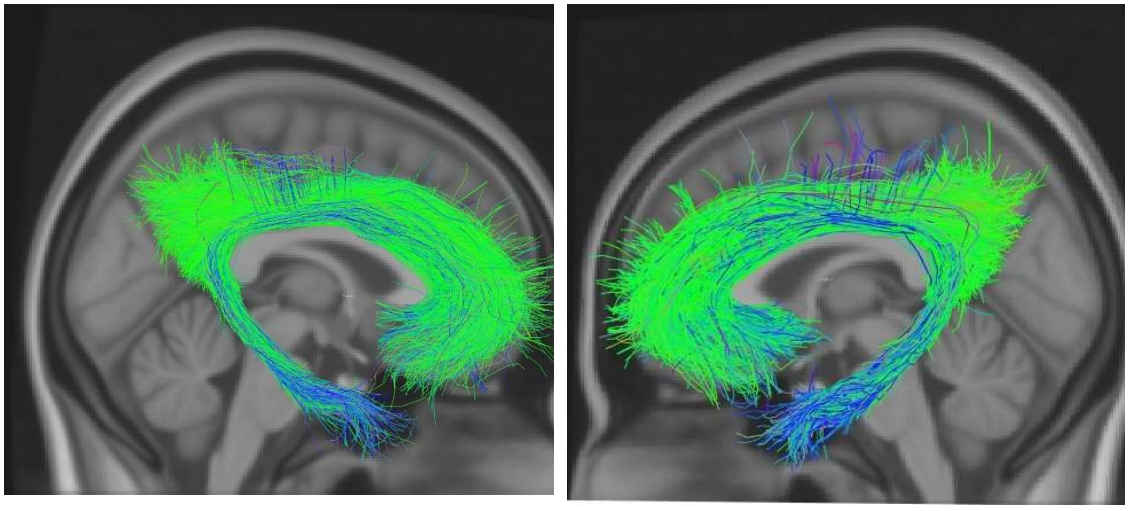


Figure 118 Megatrack Cingulum

7.19.3 Frontal aslant tract

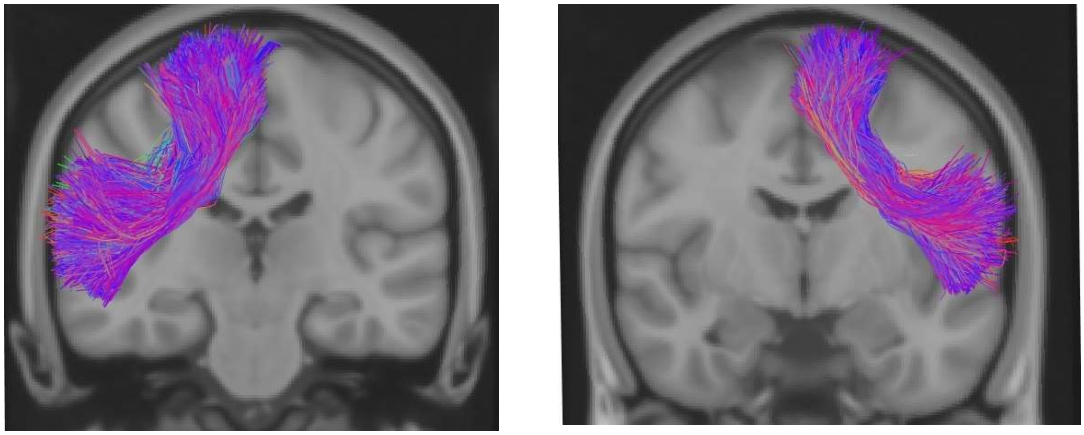


Figure 119 Megatrack FAT

7.19.4 Inferior Fronto-Occipital Fasciculus

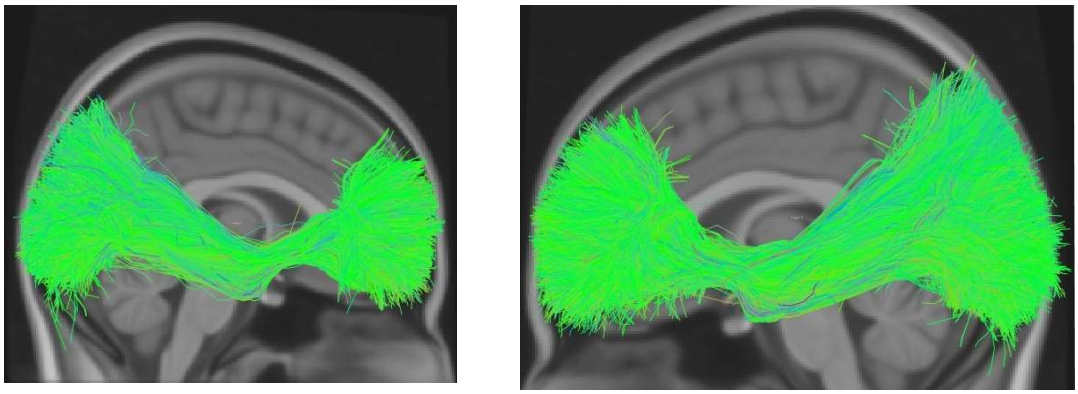


Figure 120 Megatrack IFOF

7.19.5 Superior Longitudinal Fasciculus I

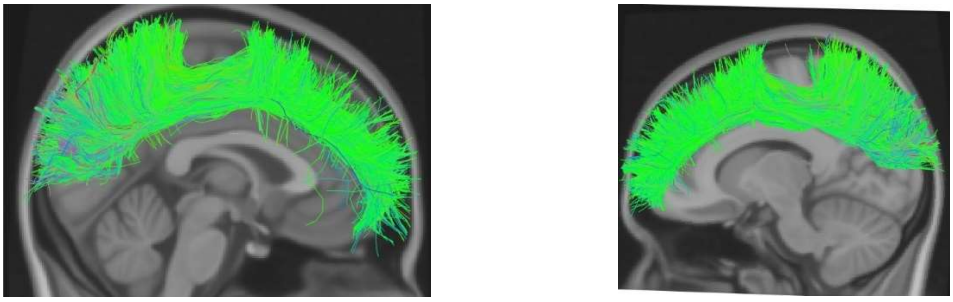


Figure 121 Megatrack SLF I

7.19.6 Superior longitudinal fasciculus II

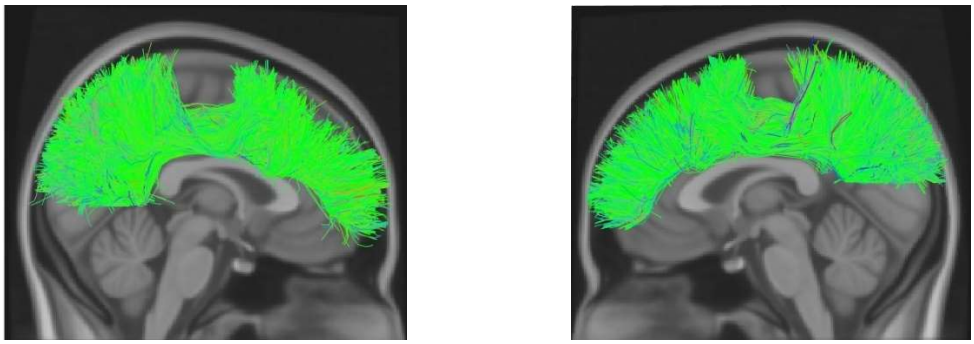


Figure 122 Megatrack SLF II

7.19.7 Superior Longitudinal Fasciculus III

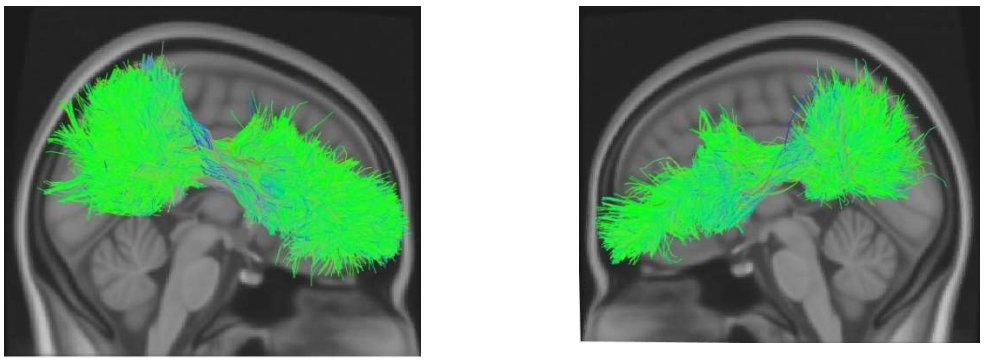


Figure 123 Megatrack SLF III

7.19.8 SLF System

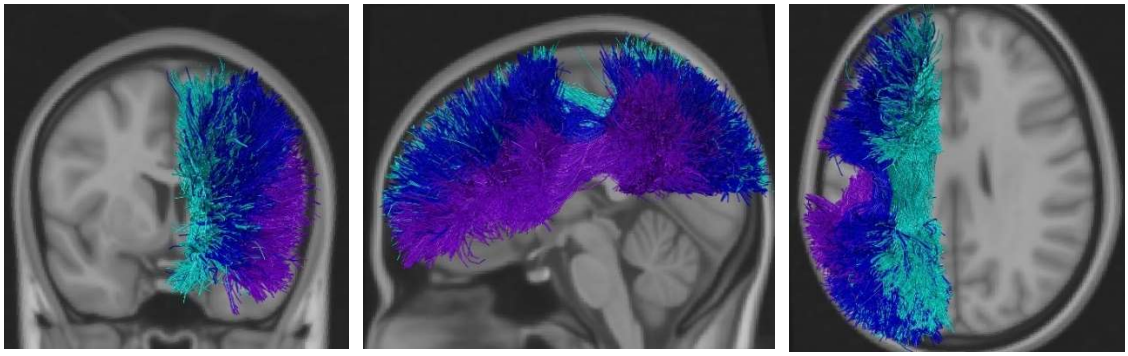
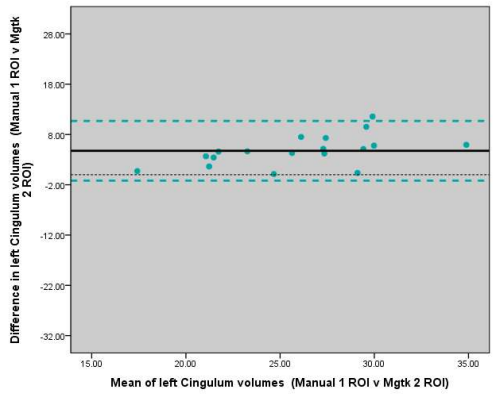
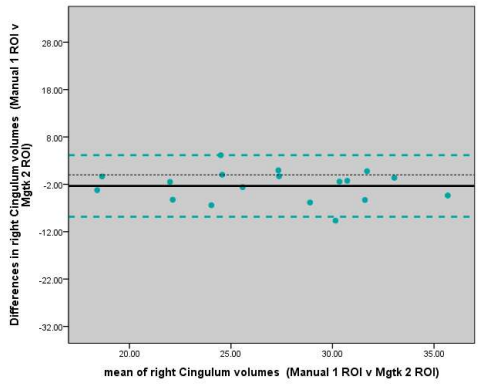


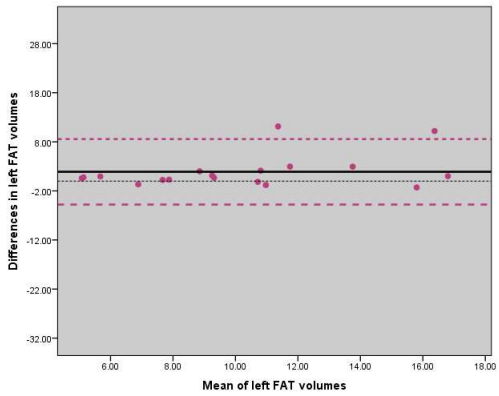
Figure 124 Megatrack SLF system

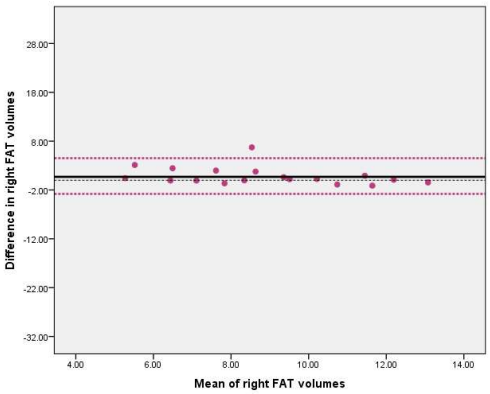
Appendix G Bland Altman plots

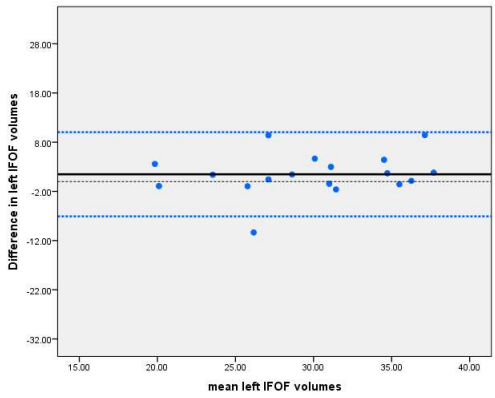
Figure 125 Bland Altman plots for tract volumes between manual and semi automated methods

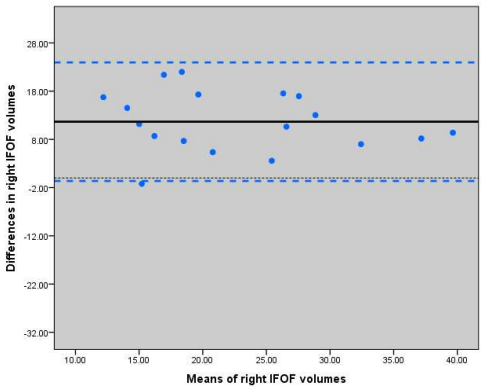


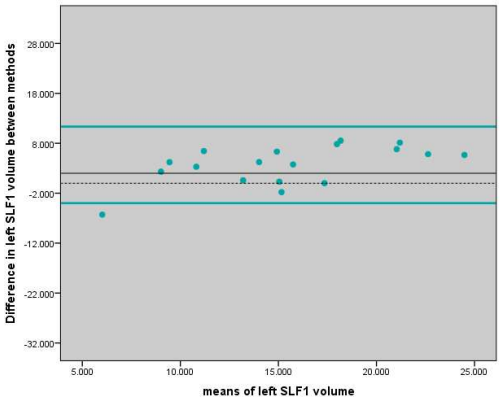


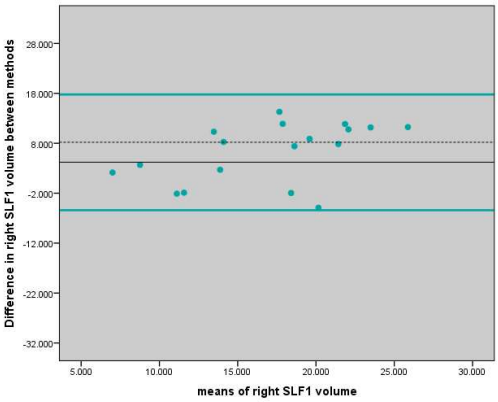


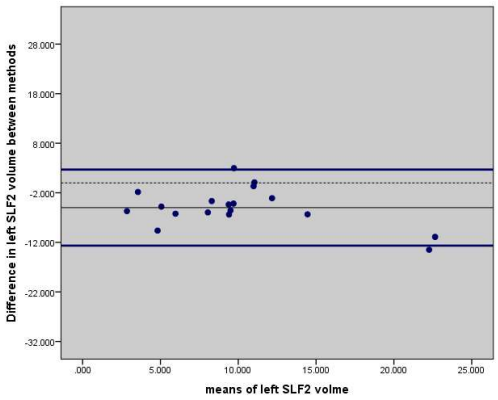


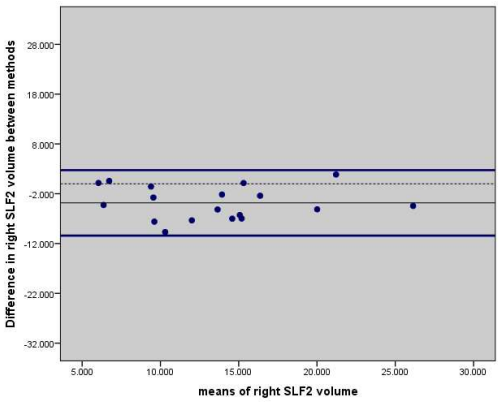


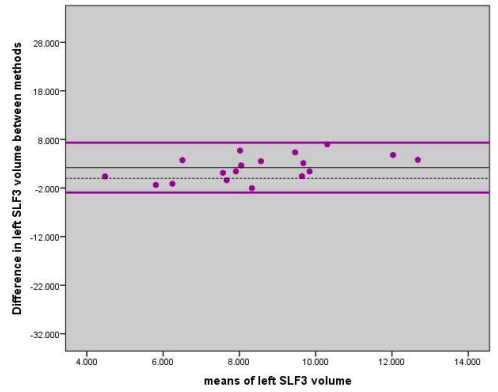







Difference in left SLF2 volume between methods
28.000
18.000
8.000
-2.000
-12.000
-22.000
-32.000
.000
5.000
10.000
15.000
20.000
25.000
means of left SLF2 volme


Difference in right SLF2 volume between methods
28.000
18.000
8.000
-2.000
-12.000
-22.000
-32.000
5.000
10.000
15.000
20.000
25.000
30.000
means of right SLF2 volume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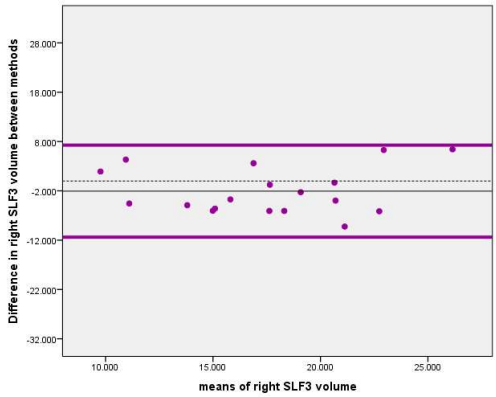
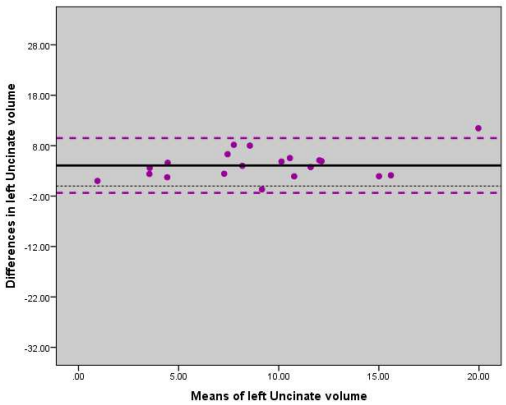
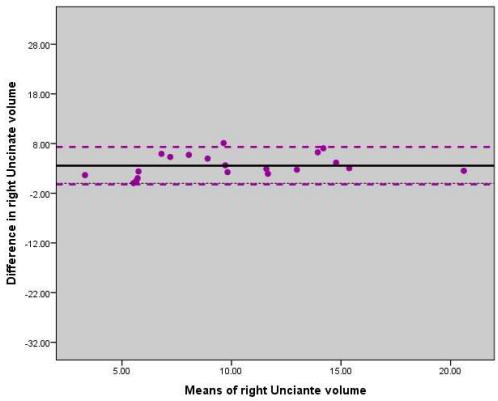
8.000
-2.000
-12.000
-22.000
-32.000
4.000
6.000
8.000
10.000
12.000
14.000
means of left SLF3 volume


Difference in right SLF3 volume between methods
28.000
18.000
8.000
-2.000
-12.000
-22.000
-32.000
10.000
15.000
20.000
25.000
means of right SLF3 volume


Differences in left Uncinate volume
28.00
18.00
8.00
-2.00
-12.00
-22.00
-32.00
.00
5.00
10.00
15.00
20.00
Means of left Uncinate volume


Difference in right Uncinate volume
28.00
18.00
8.00
-2.00
-12.00
-22.00
-32.00
5.00
10.00
15.00
20.00
Means of right Unciante volume

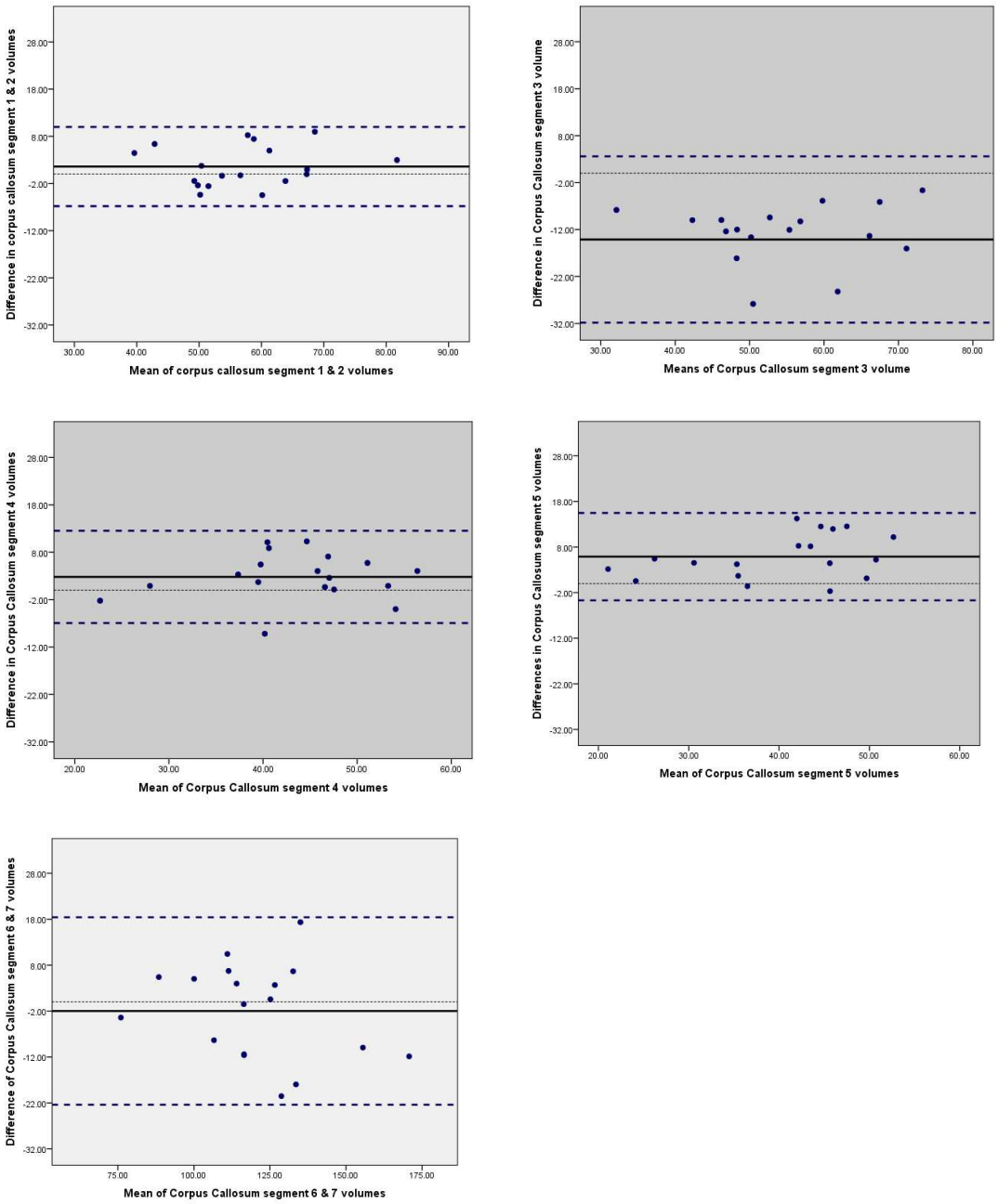
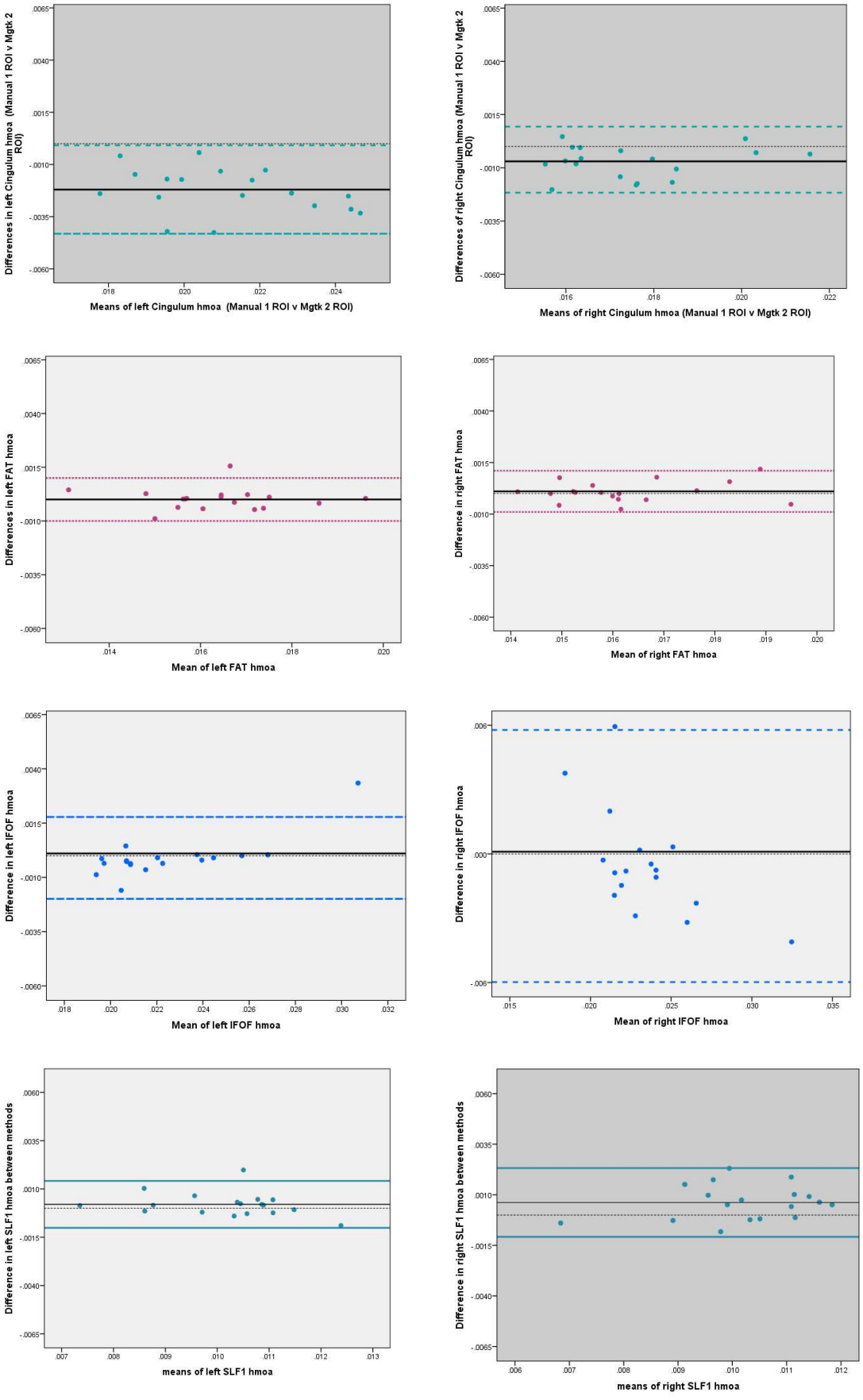
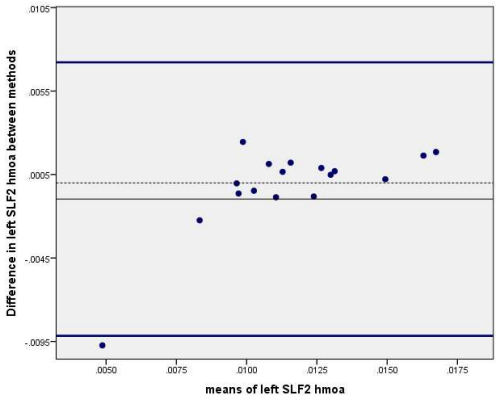
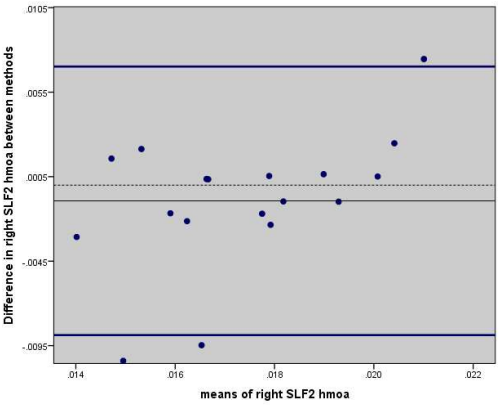


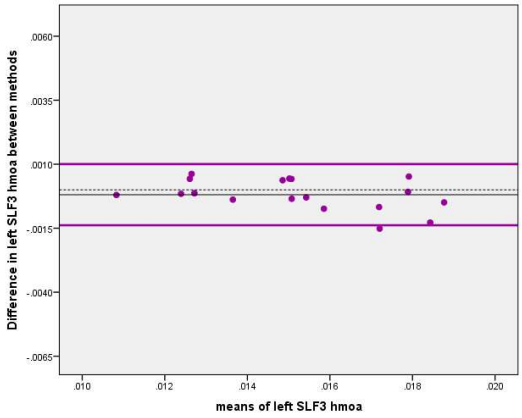
Figure 126 Bland Altman plots for corpus callosum segment volumes between manual and semi-automated methods

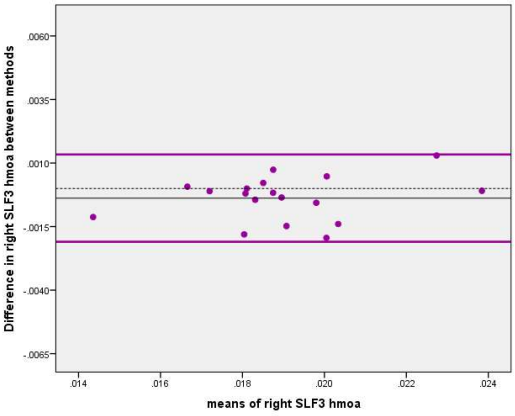
Figure 127 Bland Altman plots for tract HMOA values between manual and semi automated methods

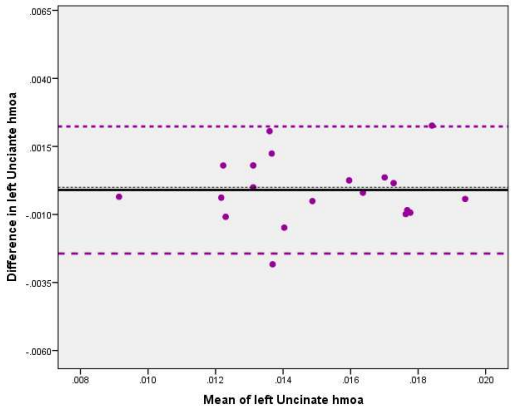



Difference in left SLF2 hmoa between methods
means of left SLF2 hmoa


Difference in right SLF2 hmoa between methods
means of right SLF2 hmoa


Difference in left SLF3 hmoa between methods
means of left SLF3 hmoa


Difference in right SLF3 hmoa between methods
means of right SLF3 hmoa


Difference in left Unciante hmoa
Mean of left Uncinate hmoa

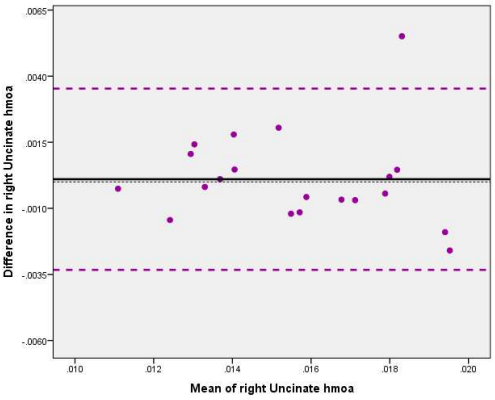
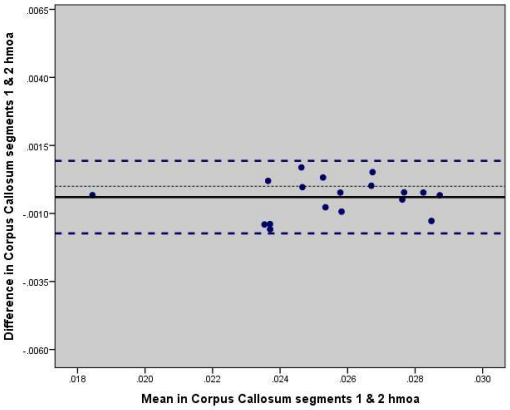
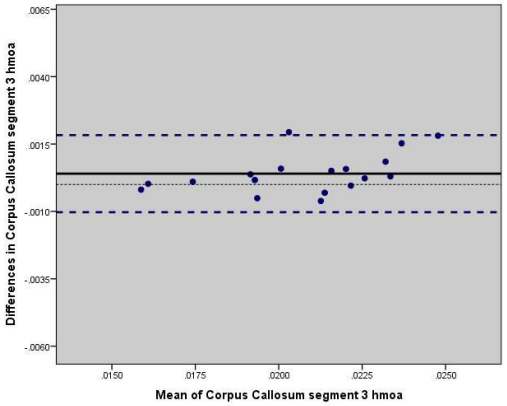
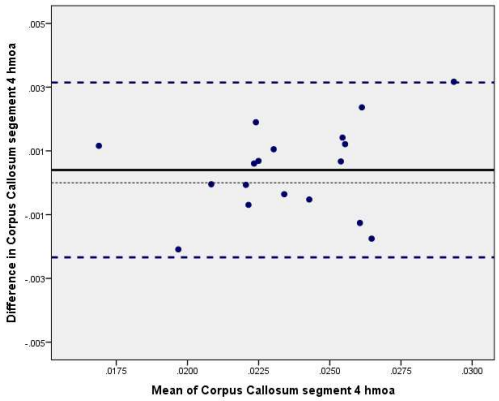
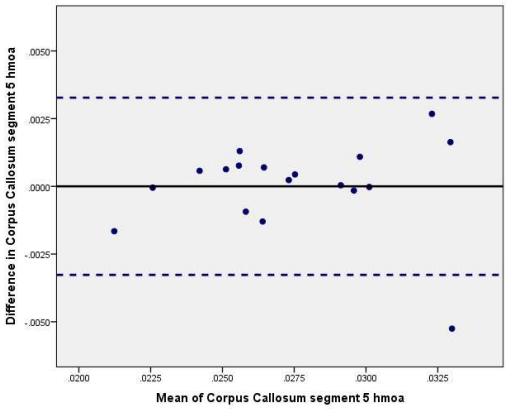

Difference in right Uncinate hmoa
Mean of right Uncinate hmoa

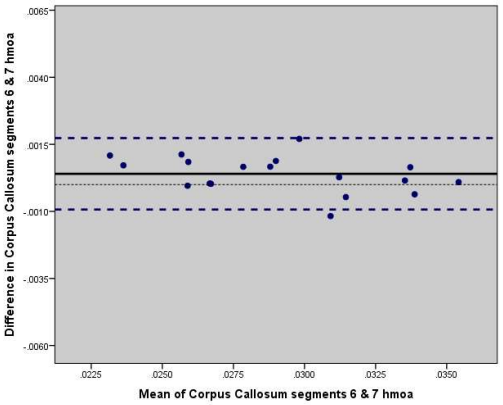
Figure 128 Bland Altman plots for corpus callosum segment HMOA values between manual and semi automated methods











Appendix H Correlations of HMOA, task performance and age

7.20 Executive function task performance and age regression

Table 32 Task performance and age correlations

Task	R	R^2	ß	Sig	F-ratio	Sig
Color-word remapping	0.469	0.220	-.469	0.000	23.706	0.000
Spatial Span	0.499	0.249	-.499	0.000	27.804	0.000
Feature Match	0.433	0.188	-.433	0.000	19.410	0.000
Spatial planning	0.448	0.200	-.448	0.000	21.066	0.000
Paired associates	0.337	0.113	-.337	0.002	10.728	0.002
Self-Ordered Search	0.316	0.100	-.316	0.002	9.334	0.003

95% CI,

7.21 White matter microstructure properties and age

Table 33 Tract HMOA and age (log10 transformed) correlations

Tract / Segment	R	R^2	ß	F-ratio	Sig
cingulum Left	0.361	0.130	-0.004	12.591	0.001
cingulum Right	0.201	0.040	-0.002	3.542	0.063
CC1&2ROS-GEN	0.246	0.061	-0.004	5.425	0.022
CC3ROB	0.054	0.003	0.014	0.250	0.618
CC4ANT	0.124	0.015	0.032	1.318	0.254
CC5POS	0.104	0.011	0.002	0.000	0.342
CC6&7ISTSPL	0.138	0.019	0.022	1.637	0.204
FAT Left	0.261	0.068	-0.003	6.129	0.015
FAT Right	0.422	0.178	-0.004	18.216	0.000
IFOF Left	0.503	0.253	-0.008	28.420	0.000
IFOF Right	0.334	0.112	-0.005	10.559	0.002
SLFI Left	0.147	0.022	-0.001	1.858	0.176
SLFI Right	0.238	0.056	-0.002	5.023	0.028
SLFII Left	0.111	0.012	-0.001	1.051	0.308
SLFII Right	0.328	0.107	-0.005	10.115	0.002
SLFIII Left	0.296	0.088	-0.003	8.061	0.006
SLFIII Right	0.401	0.161	-0.005	16.082	0.000
uncinate Left	0.327	0.107	-0.004	10.029	0.002
uncinate Right	0.252	0.063	-0.084	5.684	0.019

95% CI, Corrected for multiple comparisons: 0.05 / 19 = 0.0026

Appendix I Mediation analysis

7.22 Left uncinate and spatial planning

Aim – C is greater than C'

- (path c) (**Total effect model**) X predicts Y is significant: *F (df 1, 84) =21.066 , p = < 0.005, R^2 .20, b = -2.346, t (84) = -4.590 , p = < 0.005*
- (path a) X predicts M is significant; *F (df 1,84) = 10.029, p = < 0.005, R^2 = .11; b = -0.004, t (df 84) = -3.167 p = < 0.005*
- X and m together predict y: *F (df 2, 83) = , p= < 0.005, R^2 =*
    - (path b) M variable predicts Y: b = 88.169, t (83) 2.049 , p = < *0.05*
    - (path c') X predicts Y, including M: b = -1.991 t (83) = -3.751, p = *<0.005.*

  Mediation effect = C (coefficient) - C' (coefficient) = -2.346 – -1.991 = -.355, Lower CI -0.965 Upper CI -0.035

7.23 Left cingulum and paired associates

1. (path c) X predicts Y is significant: *F (df 1, 84) = 10.73, p = < 0.005, R^2 .11, b = -1.810, t (84) = -3.27, p = < 0.005*
2. (path a) X predicts M is significant; *F (df 1,84) = 12.59, p = < 0.005, R^2 = 0.13; b = -0.0044, t (df 84) = -3.548*
3. X and m together predict y: *F (df 2, 83) =9.78, p= < 0.005, R^2 = .19*
    - (path b) M variable predicts Y: b = 130.572, t(83) 2.82, p = < *0.05*
    - (path c') X variable no longer predicts Y or is less than Y: b = -1.230, t(83) = -2.16, p = *<0.05.*

C (coefficient)- C' (coefficient) = -1.810 - -1.230 = -0.58, Lower CI –1.252, Upper CI -0.153

7.24 Left IFOF and paired associates

1. (path c) X predicts Y is significant: *F (df 1, 84) = 10.728 , p = < 0.00, R^2 .11, b = - 1.810, t (84) = -3.275, p = < 0.005*
2. (path a) X predicts M is significant; *F (df 1,84) = 28.419, p = < 0.005, R^2 = .25; b =-0.008, t (df 84) = -5.331*
3. X and m together predict y: *F (df 2, 83) = 8.067, p= < 0.005, R^2 = .16*
    - (path b) M variable predicts Y: b = 90.073 , t(83) 2.215, p = < *0.05*
    - (path c') X variable no longer predicts Y or is less than Y: b = -1.114, t(83) = -1.782, not significant

C (coefficient) -1.810 - C' (coefficient) = 1.114 = -0.696, Lower CI 1.526 Upper CI - -0.051